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CARACTERÍSTICAS CLÍNICAS E PSICOSSOCIAIS PREDISPONDO À ACEITAÇÃO PELA MULHER DA HISTEROSCOPIA AMBULATÓRIA: UM ESTUDO OBSERVACIONAL

PSYCHOSOCIAL AND CLINICAL CHARACTERISTICS PREDICTING WOMEN'S ACCEPTANCE OF OFFICE HYSTEROSCOPY: AN OBSERVATIONAL STUDY

Tese apresentada à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Doutor em Ciências e Tecnologias da Saúde – Especialização em Decisão Clínica, realizada sob a orientação científica da Doutora Vera Afreixo, Professora Auxiliar do Departamento de Matemática e do Instituto de Biomedicina do Departamento de Ciências Médicas, da Universidade de Aveiro e do Doutor José Alberto da Fonseca Moutinho, Professor Auxiliar da Faculdade de Medicina da Universidade da Universidade da Beira Interior

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O tema que elegi tem a ver com a prática clínica diária em que me confrontava com a dor durante a histeroscopia que, para algumas mulheres, parecia difícil de suportar ou até intolerável. Fiquei convencido da bondade e interesse deste estudo com os primeiros resultados. Chegámos a algumas conclusões interessantes, cientes de que a investigação deve ser prosseguida, mas podemos dizer que satisfeitos pelo muito que aprendemos.

Disse o poeta Pessoa que "Tudo vale a pena se a alma não é pequena".
Acrescentaria eu que a grandeza da alma não estará necessariamente na capacidade de chegar a um destino, mas talvez no aceitar percorrer um caminho de resultados incertos, apreciando as dificuldades, rejubilando com as pequenas vitórias e sentindo a angústia e incerteza próprias das coisas imprevisiveis, como é o caso da investigação.
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António Santos Paulo

Palavras-chave Histeroscopia de ambulatório, mini histeroscopia, histeroscopia convencional, avaliação da dor, anxiedade, fatores de risco, controlo da dor, inquéritos de satisfação e anestesia histeroscópica

Resumo

A histeroscopia é hoje uma técnica imprescindível em ginecologia quer no diagnóstico de alterações genitais superiores, quer no tratamento minimamente invasivo, sendo segura, fiável e com poucos efeitos secundários e complicações. A miniaturização dos aparelhos juntamente com aperfeiçoamento técnico (nomeadamente com a abordagem vaginoscópica, sem recurso a espéculo, nem a tração do colo) vieram permitir o seu uso em consultório. Usado sem anestesia reduz os riscos do internamento e tornam o exame acessível; tem contudo a limitação da dor provocada pela instrumentação. Apesar de muitas tentativas analgésicas e anestésicas, o controlo da dor não é satisfatória em algumas doentes nas quais a histeroscopia é difícil de suportar.

Este trabalho pretende estabelecer se a dor é menor com os mini histeroscópios do que com os instrumentos convencionais, avaliar quão grave é o problema da dor (quantificando a proporção de mulheres que se queixam) mesmo com este aparelhos mais delgados e tentar saber se existem fatores de risco que favoreçam a dor, ou que pelo contrário protejam a doente. Também se pretende estabelecer se os inquéritos de satisfação às doentes se correlacionam com a pontuação de dor e se a ansiedade interfere com as queixas álgicas. Finalmente também tentámos investigar se uma técnica nova de anestesia local, administrada através do histeroscópio com recurso a uma agulha cistoscópica, reduz a dor e torna o exame mais tolerável.

Os resultados mostraram haver redução estatisticamente significativa da perceção da dor com mini histeroscópios em relação a aparelhos convencionais. Mostraram ainda que mesmo com calibres finos há uma proporção de doentes entre 13 e 30% que ainda refere dor moderada a severa e que reduzir o calibre abaixo dos 3,5mm pode não resultar numa redução maior da dor. Quanto a fatores de risco para a dor os nossos resultados não encontraram relação, exceto uma proteção na dor para as doentes obesas, que relacionamos com uma maior impregnação hormonal (androgénica e por via da aromatase, estrogénica). A ansiedade não parece ser importante na dor sentida, ainda que exista uma pouco significativa relação entre traço ansioso e intensidade da dor relatada. No que se refere aos questionários de satisfação, correlacionam-se muito bem com a dor reportada, tendo uma boa sensibilidade e especificidade; sendo simples de administrar e fáceis de interpretar poderiam provavelmente substituir as escalas da dor e ser úteis para eventual seleção das doentes a quem administrar a anestesia local histeroscópica. Finamente a técnica histeroscópica de injeção local de anestésico reduz significativamente a dor e poderá ser uma solução para tornar a intervenção suportável em ambulatório.

Keywords Office hysteroscopy, mini-hysteroscopy, conventional hysteroscopy, pain evaluation, anxiety, risk factors, pain control, satisfaction questionnaires and hysteroscopic anaesthesia

Abstract

Hysteroscopy today is an essential tool in gynaecology both for diagnosis of female upper genital tract abnormalities and for minimally invasive surgery procedures. It is safe, reliable and has few side effects and complications. Diminishment of instrument diameter together with technical improvements (such as the vaginal "no touch" approach without use of speculum or cervical traction) has allowed procedures in office environment. Used without analgesia or aneasthesia it has reduced hospitalization risks and made the examination affordable; it has a drawback which is the level of pain some women refer with instrumentation. Although many attempts with the use of analgesics and anaesthetics have been made, pain control is not satisfactory in some patients for whom hysteroscopy is hard to endure.

In this work we aim to establish if pain reporting is lower with mini-hysteroscopes compared to conventional scopes, how big is the problem "pain" (quantifying the proportion of women still complaining) even when using the slender mini-scopes and try to establish if there are risk factors which might influence pain reporting, or on the contrary protect, women from agony. We also explored if satisfaction questionnaires correlate well with pain scores and if patient anxiety interferes with pain. Finally we have investigated if a new local anaesthetic administration technique, with the use of a cystoscopic needle through the hysteroscope, can reduce pain and make the procedure more tolerable.

Our results show there is a statistically significant reduction of pain scores when using mini-hysteroscope compared to conventional instruments. They also show that even using smaller caliber scopes there is a proportion of women varying from 13 to 30% who will still complain of moderate to severe pain and that reduction of scopes below 3.5mm diameter may not reduce pain scores any further. As to risk factors for pain, our results have not found relation to pain with risk factors except for some protection for pain in women with high body mass index, and we relate this finding with elevated circulating hormones (androgens which are peripherally converted to estrogens via aromatase in adipose tissue). Anxiety does not seem important in pain reporting, even if a slight statistical significance was found between anxiety trait and pain reporting. As to satisfaction questionnaires, they seem to correlate well with the pain experience and show and excellent sensitivity and specificity: simple to administer and easy to interpret, they could probably replace more complicated pain rating scales and be useful in selecting women who would benefit from local anaesthesia. Finally as to the new technique of applying local anaesthetics "hysteroscopic anaesthesia", results show a statistical reduction of pain after injection and it could become a practical solution in making hysteroscopy bearable in an office setting.

Contents

Abbreviations

Body mass index	BMI
Carbon dioxide	CO2
Cyclooxygenase	COX
Endometrial Laser Ablation	ELA
Intramuscular	IM
Light amplification by stimulated emission of radiation	laser
Local anesthetic systemic toxicity	LAST
Mean differences	MD
Nonsteroidal anti-inflammatory drugs	NSAIDs
Numeric Rating Scale	NRS
Office Hysteroscopy	OH
Prospective Trials	PT
Randomized Controlled Trials	RCT
Receiver Operating Characteristic	ROC
Rostral medial medulla	RVM
Serotonin-norepinephrine reuptake inhibitors	SNRI
State Anxiety-Trait Inventory for Adults	STAI
Trans Cervical Resectoscopic Ablation	TCRA
Transcutaneous electrical nerve stimulation	TENS
Tricyclic antidepressants	TAD
Visual Analogue Scale	VAS
World Health Organization	WHO
Yttrium Aluminum Garnet	YAG

PART 1- INTRODUCTION

1 Hysteroscopy

1.1 What is hysteroscopy?

Hysteroscopy is a procedure used for diagnostic purposes or for minimally invasive surgery, and is performed with endoscopes [1]. They can be flexible or rigid rods with diameters ranging from 3.1mm to 5mm (for outpatient office diagnostic and minimally invasive surgery) to 10mm outer sheet diameter scopes (appropriate for ressectoscopic surgery under general anaesthesia for these larger hysteroscopes require mechanical cervical dilatation which is painful).

The device, whichever it´s calibre, has a lens system, a working channel all along its length for use with hysteroscopic instruments (forceps, scissors and various electrodes and probes) as well as for distension media flow (which can be carbon dioxide or various liquid media). Recently normal saline has substituted most liquid media for its safety and because new bipolar electric probes work in this media.

The hysteroscope (figures 1 and 2) is operated by inserting the rod through the vagina, tackling the cervical canal and entering into the endometrial cavity. The aim is to provide a panoramic view of the upper genital tract through an eyepiece, which in modern apparatus is attached to a camera, and images can be displayed on a screen. Photographs and videos can be taken and recorded, stored for future visualization and comparison or specialist training. Finally to be able to view images, a light source must be attached.

Figure 1 – unattached hysteroscope

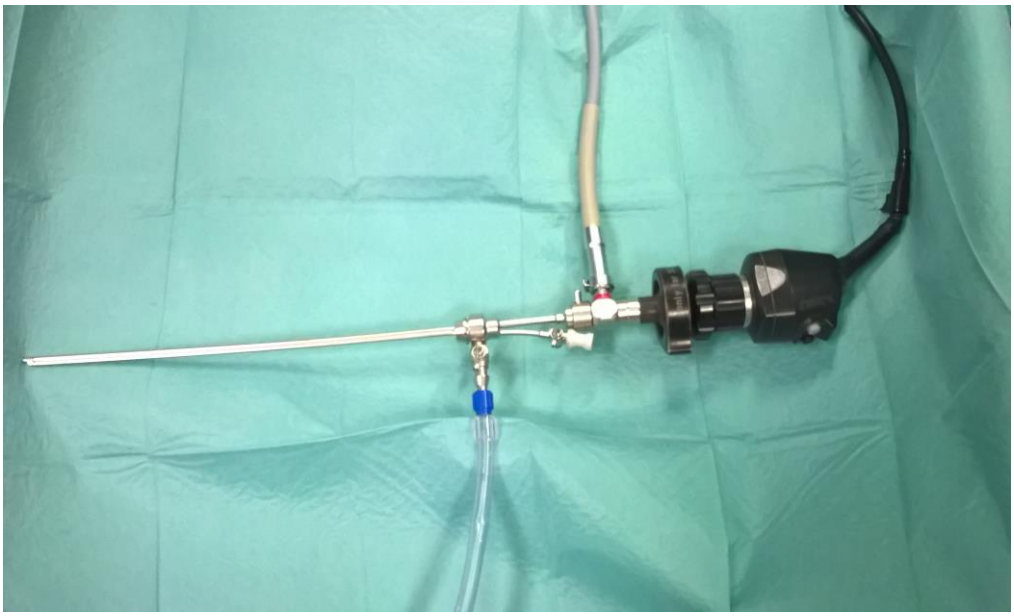


Figure 2 – fully attached hysteroscope ready for use

1.2 Evolution of hysteroscopy: Development

The first ever use of the concept of examining body cavities with the aid of a tube is attributed to Phillip Bozzini, a German physician, in 1806. The contraption was no more than a box with a candle light with two attachments: an eye piece on one side and a collection of interchangeable hollow pipes at the other end. Dr Bozzini placed a mirror inside the box to reflect the light into the pipes, allowing illumination from the flame of a candle stick to the interior of the bodily orifices [1, 2].

Almost fifty years later, in 1853, Désormeaux used a lamp burning turpentine and alcohol with a chimney attached to an optical-like tube, calling this apparatus "endoscope". This strange looking instrument had reflecting mirrors and condenser lenses which increased lighting and was used for urological examinations and treatments, becoming not only a diagnostic instrument, but also a promising therapeutic tool [1, 3].

Pantaleoni is credited as the first to use such an instrument in female care in 1869. He diagnosed an endometrial polyp as the source of abnormal uterine bleeding and treated it by cauterizing with silver nitrate. [4]. However, visualization of the uterine cavity through this hollow tube was hard as the uterus is not very distensible and uterine mucosa tends to bleed, compromising direct visualization.

The German physician Nitze was responsible for modernizing the endoscope and creating the cystoscope in 1877. He sealed off the extremities with lenses and attached lighting to the far end of the rod using a platinum wire loop; this apparatus was subsequently introduced into the bladder distended by water. Later innovations in 1879 included filament lighting by miniaturizing Edison's electric bulb invention [1].

1.3 Technical Improvements: Contact Hysteroscopy

The first examinations of the utero were made without expanding the cavity — *contact hysteroscopy* —, the same technique used by Desormaux [3]. On the other hand, Pantaleoni was the first to perform the examination on a living person [4].

Following initial generalized disappointment with "panoramic" examinations due to media distension issues, Marleschki in 1962 had suggested that returning to contact hysteroscopy could be of value [5]. He introduced an instrument with a 12.5 magnification power and inaugurated micro hysteroscopy, a device with which one is able to observe details at the scale of the cell; it is still of utility in gynaecological practice [6]. A few years later in 1972 Vulmiere patented a device for *contact hysteroscopy* [7].

Constant modernization and the quest for better diagnostics, global visualization and operating conditions, brought about the issue of distension of the walls of the womb as a necessity for quality examinations.

Nonetheless, in the 1980's, Hamou presented yet still one more *contact* apparatus with magnification adequate for microcolpohysteroscopy — histology studied in the living person [5, 8]. But the idea subsequently lost followers. Nowadays there are still authors who find usefulness in the device, particularly as a complementary study to *panoramic* hysteroscopy [5].

1.4 Distension and panoramic Hysteroscopy

The pursuit for global visualization of the cavity implied distension and various attempts were made. Distension devices were conceived and the new tools for *panoramic hysteroscopy* gained the preference of gynaecologists.

In 1925, Rubin initially used air and then carbon dioxide for this objective. Many physicians including German pioneers such as Mikulicz-Radecki preferred low viscosity fluids [9]. In 1928, Gauss [10] was the first to use water, but reported bleeding and the mixing of blood, which hindered vision. A second problem referred by Gauss, Schroeder and Segond was fluid passage to peritoneum and blood stream, which could cause vascular overload [9]. Schroeder established minimum intra-uterine pressure for visualization in panoramic hysteroscopy around 25 to 30 millimetres of mercury (mmHg). Until the sixties and seventies, no great change occurred in hysteroscopy and various authors used instruments similar to Gauss, Schroeder and Segond with in and outflow of fluids [9]. Since 1970 Lindemann worked in perfecting carbon dioxide inflators for hysteroscopy [11]. Still popular in office settings, recent data seem to support this media use for diagnostic purpose [12]. Also in the 1960's, pioneers experimented hysteroscopy with rubber balloons but this method didn't allow biopsies and was soon abandoned [13].

Edstrom and Fernstrom, in 1970, experimented with pumps delivering high viscosity liquid media non-miscible with blood [14]. Although they provide good quality viewing even with haemorrhage, there are safety problems and technical difficulties associated with their use. As to low viscosity fluids, the electrolyte free fluids such as 1.5% glycine, 3% sorbitol and 0.5% mannitol all provide excellent visibility [15]. However, they also have complex safety restrictions and it would be wise to discontinue their use. Glycine, in particular, apart from cautions, is nonconductive and would seem adequate for mono-polar electro-surgery, so debate remains about its utility [15].

Finally, there are normal saline and other electrolytes containing media which are safe for patients, although inadequate for mono-polar surgery [15]. Fortunately, the development of bi-polar electrodes that work in saline solutions, have been made available for use in gynaecological care. The American Association of Gynecologic Laparoscopists - AAGL has issued guidelines in which it questions the usefulness of some of these media nowadays, mainly high viscosity media [15]. A summary of the existing distension media in use is given in Table I, along with the advantages and disadvantages of each choice.

Table I

Issues and cautions with distention media

Distension Media	Characteristics of media
CO2	Only diagnostic; may increase patient discomfort
High viscosity fluid (32% dextran 70)	Allergic reaction, coagulopathy, vascular overload, caramelize on instruments rendering them useless
Low viscosity fluid (3% sorbitol, 1,5% glycine, 5% mannitol)	Good for monopolar, may cause severe fluid and electrolyte disturbance, with life threatening hyponatremia and hypo osmolality, especially dangerous in pre-menopausal women
Normal saline	Safe media, does not cause electrolyte imbalance, adequate for bipolar electrodes

1.5 Optics and Lighting

The first great improvement in lighting conditions was brought by a miniaturized version of Edison's light bulb, fitted at the tip or far end of the rod. In 1952, Fourestier replaced the glass in the endoscope for a full size 1.5 mm diameter quartz rod encased by a steel sleeve and having a total of 2 mm diameter; this light guide was introduced into a rigid endoscope with a 15 V lamp and condenser lens at the proximal end. The instrument transmitted a clear filtered light into the body cavities. Although the optical quality was excellent, the apparatus was awkward to use [1].

In 1955, Hopkins, a physician keen on physics, [16] replaced the classic thin glass lenses of the Nitze endoscope for a total length rod of coherent optic grade glass (optic fibres) instead of small lenses separated by air and revolutionized endoscopes bringing a clear amelioration in lighting [17]. A further added advantage was the reduction of endoscope diameters, leading to the invention of a paediatric cystoscope [1]. Around 1959 Karl Storz manufactured the first complete set, initiating the golden age for rigid instrument endoscopy [17]. Vulmiere, in 1972, patents a much elaborated endoscope using a continuous glass fibre rod, allowing both illumination and observation and with two options: direct vision and lateral vision [7]. His endoscope was soon coupled with glass fibre connections, allowing the use of powerful external "cold light" source, thus revolutionizing endoscopy.

1.6 Surgery and Hysteroscopy

The first ever gynaecological treatment through an endoscope is attributed to Pantaleoni [4]. As technique evolved with better and slender endoscopes, so did surgical tools and options. Norment was quite an innovator and, in 1957, it seems to have been his idea, to fit a resecting loop, at the tip of his endoscope for polyp excision [18]. A decade later, Neuwirth reports a successful monopolar loop resection of sub mucous leiomyoma with a urologic resectoscope [9, 19, 20]. So begins a new era in surgical endoscopic care in gynaecology.

Goldrath used Yttrium Aluminium Garnet (YAG) laser to successfully perform endometrial ablation in 1981 [21] and such works were rewarded by the FDA's approval of YAG laser in 1986. Valle published his results on endoscopy surgery in 1990, using various methods including electrocoagulation, rigid and semi-rigid scissors and forceps, transection of the pedicle and dissection plus enucleation of myomas primarily for treatment of infertility [22]. Electro surgery was developing quickly, using loop resection and rollerball coagulation which were cheaper and equally effective, so in 1989 the health care regulator also approved resectoscopy for the same indications, namely symptomatic endometrial polyps and leiomyomas [23, 24].

At the turn of the XXI century in his editorial "Endometrial resection and ablation: past, present and future" published in Gynaecological Endoscopy, David Parkin from Aberdeen summarizes the State of the Art [25]. He elaborates on available techniques such as Endometrial Laser Ablation (ELA) and compares it to Trans Cervical Resectoscopic Ablation (TCRA). Results were expressed on patient satisfaction for heavy bleeding control and he finds that both methods lead to dramatic decrease in the need for hysterectomy. He is sceptical about alternative and emerging endometrial destruction methods, such as thermal balloon and microwave, but he recommends randomized controlled trials. Indications are systematized, prognostic factors are pointed out and the importance of using guidelines is stressed. Finally he expresses concerns about adequate training of endoscopic gynaecologists and establishes perspectives for the evolution of endoscopy. He also suggests that pharmacological preparation prior to surgery could enhance success [25].

Ten years later, in 2010, Umranikar reviews indications, equipment options and techniques and compares results between first generation (TCRA, rollerball and laser) and second generation (thermal laser, hydro ablator, cryoablation, microwave ablation, electrode ablation, and impedance controlled bipolar radiofrequency ablation) techniques [26]. He concludes that results, as well as patient satisfaction, were comparable and distinguishes two major treatment goals: bleeding control and infertility treatment. Pointing out the importance of classifying sub mucous fibroids according to The European Society of Hysteroscopy score, he argues that such classification has a prognostic value on treatment strategy. As to the novel treatment option, *impedance controlled bipolar radiofrequency ablation* proposed by Gallinat [27], he agrees that it is effective, safe and seems promising for less experienced hysteroscopic surgeons.

In 2013, Emanuel published a paper similar to Umranikar's in 2010, generally sanctioning the same points of view. He does, however introduce a new *morcellation* instrument tested by Van Dongen [28] and described by Cohen [29], seemingly easier to use even by less experience surgeons. It is expected to cut operating time so it should be an instrument with a bright future in hysteroscopy [30].

1.7 Hysteroscopy today

Hysteroscopy allows direct visualization of the cervical canal and endometrial cavity. As a diagnostic device it is very useful in investigating uterine abnormal bleeding where it is considered the gold standard [31-36]. Its objective is the examination of the female upper genital tract through direct visualization of the cervical canal and endometrial cavity frequently leading to the discovery of unsuspected pathologies, such as polyps and fibroids [37].

Hysteroscopy allows diagnosis of endometrial hyperplasia and cancer [38, 39] and permitting histological sampling, it confirms the nature of lesions [40-42]. Endometrial biopsy may even be useful in cancer staging by ruling out cervical involvement [43-45]. Also, successful attempts have been made to use hysteroscopy for the sentinel node technique in endometrial malignancy [46, 47], to identify which nodes are involved and tailoring the surgery to patient's needs. Concerns about spreading neoplastic cells into the peritoneum with hysteroscopy [48] may not be justified, as the procedure appears to be safe [47, 49, 50].Foreign bodies can be detected and retracted with adequate tools [51]. Or, on the other hand, inserted into the fallopian tubes, for instance, for sterilization purposes [52-54]. Some authors consider hysteroscopy essential in routine work up of infertile women [55-57], revealing unsuspected intra uterine mass, adhesions and mullerian malformations [58-60].
Modern office hysteroscopes and mini-hysteroscopes, smaller in diameter (2.9mm to 5mm), avoid cervical dilation [61-63] and together with technical improvements, such as the vaginoscopic no-touch approach [64-66], have improved patient tolerance and allow the procedure to be performed without analgesia or anaesthesia [63], although pain is not completely managed [62, 67-73].
Office hysteroscopy and surgery have become popular and cost effective, treating various conditions: placental remains [74], myoma and polyp ablation [75-78], uterine septum (conventional hysteroscopy) [79, 80] and vaginal septum resection [81], and trans cervical sterilization [82] safely and at a very low cost [83].

1.8 Advantages of hysteroscopy

- Safe [23, 30, 61, 84]
- Reliable [23, 61]
- Cost effective [36, 61, 76, 85, 86]
- Very accurate in diagnosis [23, 61, 76, 86]
- Easy to perform even for less skilled operator [68]
- Allows sampling for histopathology [23, 61]
- Minimally invasive diagnostic and surgical tool [61]
- Very rapid recovery and low morbidity [61, 86]
- Gold standard tool for investigating uterine abnormal bleeding [31-36, 61, 63, 68]
- "An operative gold standard technique and an important contribution to Patient Safety" [83]

1.9 Disadvantages

- Although it is a minimally invasive technique it still requires the introduction of an endoscope into the vagina, through the cervical canal all the way into the endometrial cavity [23, 61].
- Operators need to acquire skills [61, 87, 88],
- Some patients will not easily tolerate the operation [61, 68],
- Possible complications may follow (immediate or late in onset) [23, 38, 89-91]

1.10 Indications for Hysteroscopy

Diagnosis:

- Uterine abnormal bleeding (metrorrhagia, heavy bleeding, post-menopausal bleeding) [33-35, 40, 61, 88, 92, 93]
- Infertility [37, 56-58, 61, 94-97]
- Genital malformations (septate uterus, septate vagina, septate uterus) [61, 98, 99]
- Thicken endometrium on a previous transvaginal ultrasonography [40, 61]
- Endometrial and endo-cervical cancer suspicion, staging and confirmation [46, 47, 61]

Diagnosis and treatment:

- Septate genital malformations (surgical removal) [80, 100]
- Endometrial or endo-cervical ablation of polyps or myomas [23, 24, 78, 101]
- Female sterilization (fallopian tube occlusion) [78, 102-105]
- Ressectoscopic removal and follow up of myomas and endometrial hyperplasia [22, 106-111]
- Retraction of foreign bodies in endometrial cavity (placental or embryonic remains, IUD lost in the cavity) [74, 112-117]

1.11 Complications of hysteroscopy

Hysteroscopy is very safe and complications are infrequent. However they may arise and caution should be used to avoid and treat any unforeseen difficulty [102, 118-120].
Possible complications associated with hysteroscopy (Table II):

Table II
Possible perioperative complications in hysteroscopy

Cause	Consequence
Patient positioning	Neurologic and compartment syndrome
Anaesthesia	Allergy, systemic injection, overdose
Access issues	Cervical trauma and perforation
Distending media	Fluid overload, electrolyte imbalance
Gas emboli	CO2 or air in blood vessels
Perforation	Uterus, adjacent structures (bowel, bladder, vessels)
Bleeding	Endometrium, myometrium, periuterine vessels
Electrosurgical	Local (active electrode) or remote (currant diversion) burns
Infection	Endomyometritis, peritonitis
Late complications	Adhesions, pregnancy related (uterine rupture, placenta acreta)

Cervical preparation with misoprostol before procedure facilitates operative management [121], in both menopausal [122] and premenopausal women [123]. Preparation alone will unfortunately not avert complications which may arise from various conditions and so extreme attention must be paid to technique and to possible accidents and incidents [118]. One can minimize accidents by following a strict surgical protocol, respecting indications and excluding patients who are thought high risk and ruled inadequate for the procedure [118]. Patient positioning and vital signs monitoring together with close checking of equipment are very important. It should be emphasised that the surgeon has to pay close attention to signs of incidents or accidents [118].

2. Pain

Pain can be defined as an "Unpleasant sensation associated with a specific part of the body" which makes it much more than just an automatic reaction to a nociceptive stimulus [124].

2.1 Pathophysiology of Pain [124, 125]

The Primary Afferent Nociceptor involves three different types of neurons, which are present in tissues and peripheral nerves: primary sensory afferents, motor neurons, and sympathetic postganglionic neurons. The cell bodies of primary sensory afferents are located in the dorsal aspect of the vertebral root ganglia adjacent to conjugated orifices. This cell's primary afferent axon has one branch projecting centrally into the spinal cord and another branch reaching peripherally to innervate tissues. These fibres differ in thickness, degree of myelination, and signal transmission speed.

A-beta (Aβ) large-diameter afferent fibres are present in nerves which innervate mostly the skin and essentially respond to tactile perception (soft touch or moving stimuli). These fibres do not normally respond to pain. Two other classes of primary afferents have been described: the small-diameter myelinated A-delta (Aδ) and the unmyelinated (C-fibre) axons. Aδ and unmyelinated C-fibres innervate the skin and also deep somatic and visceral structures. They all respond to high intensity mechanical stimulation and are so called *high-threshold mechano receptors* but some Aδ are responsive to both mechanical and heat stimuli (*high-threshold mechanothermal receptors).* C-fibres are slow conducting nonmyelinated and transmit nociceptive information from a broad diversity of insults (mechanical, thermal and chemical). They are designated *C-polymodal nociceptors*. So Aδ and C afferent fibres are mainly responsible for most of the pain impression, reacting to intense stimuli as primary afferent nociceptor response and when, by any reason their transmission is blocked, conduction of pain is interrupted.

The process by which free nerve endings translate a noxious insult into nociceptive impulse is called *Transduction.* The Aδ and the unmyelinated fibres show their maximal nociceptive response (painful sensation) only when strong stimuli potentially damaging processes to tissues occur. A fourth category of "silent" nociceptive fibres are also involved in *transduction* but only when (and if) inflammatory changes occur. All this process is dependant on triggering the opening of depolarization of ionic (mainly calcium inflow) and or closing (of potassium outflow) channels [125].

The second phenomenon involves *transmission* of impulse (chemical through *substance P, glutamate and Calcitonin Gene Related Peptide or CGRP*, but also electrical through membrane depolarization) by the axons from neurons located at the dorsal root ganglia of the posterior horn of the spinal cord. They are the primary afferent nerve fibres [124]. Here axons connect to numerous "second-order" spinal neurons which cross over to the contralateral side and direct the signal upward to the brain via ascending sensory pathways. However, at this spinal level, noxious stimulus automatically activate motor neurons from the corresponding ventral horn and results in reflex withdraw from insulting agent. The raw neuronal impulses are so *modulated* in the posterior horn where neurons rich in opioid receptors (mu or μ, kappa or κ and delta or δ) react to endorphins, substance P and glutamate and either enhanced or dampened the initial signal. Second-order neurons may change their response, lowering excitation thresholds and expanding receptive fields. This process called *central sensitization* may exaggerate pain and be responsible for *allodynia* and *hyperalgesia* both phenomena being harmful to the pain perception process. Ascending axons reach the thalamus and a "third-order" neuron is activated,

taking the message to the somatosensory cortex [124]. Finally this modulation is probably also controlled by descending pathways from higher central nervous system (neurons from the frontal cortex, hypothalamus and other areas) to the mid brain and spine via rostral medial medulla (RVM), contributing to pain exaggeration or inhibition.

The final result is conscious awareness or *perception* of pain which includes all four phases together with psychological characteristics of the individual. This is called the Gate Control Theory and according to this concept, the fast transmitting Aβ fibres allows the cortex to process information and forms a connection with the inhibitory interneuron activity, decreasing the neuron's chance of firing, while C fiber's synapse indirectly increase neuron's chance of firing and enhance pain [125].

2.2 Types of Pain [125]

There are in general four types of pain:

1. Nociceptive pain

This sensation is well localized, acute and finite. It results from direct stimulation of nociceptors

2. Inflammatory pain

Normally consequence of inflammatory phenomena secondary to primary injury, it is largely mediated by nonmyelinated C fibres.

3. Neuropathic pain

Caused by injury to peripheral nerves or central nervous system, it typically presents as burning or prickling, sensations accompanied by paraesthesia or dysesthesia. It is common in diabetes, tumour infiltration, and post-infection such as herpes zoster or chemotherapy.

4. Functional pain

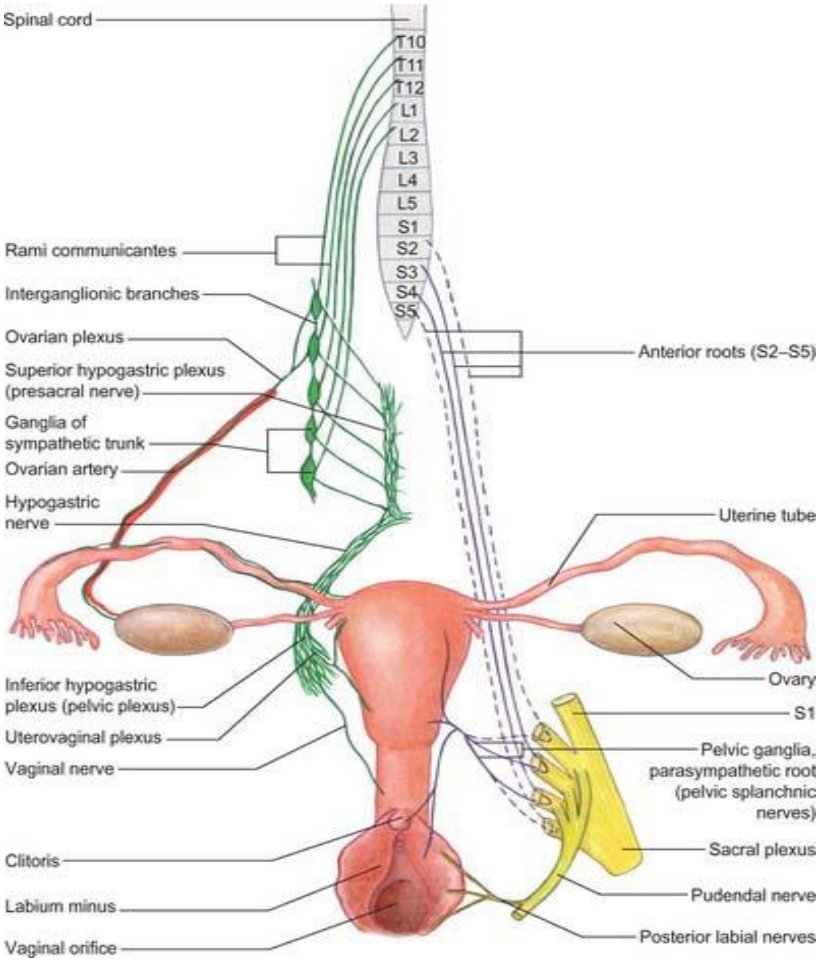
   Derived from central nervous system abnormal processing of incoming pain stimuli, is very common in chronic pain syndromes which are the result of all four types of pain. This chronicity of pain arises partially from structural neural plasticity leading to increased number of synapses [125].

2.3 Visceral Pain versus Somatic pain [126-128]

Somatic pain in generally sharp, well defined, usually consequence of cutting, perforating, blunt trauma, chemical or thermal injury. On contrast, visceral pain is ill defined, aching, dull and accompanied by noticeable autonomic symptoms (pallor, hypotension, sweating, nausea or vomiting and changes in body temperature) [126, 127]. Visceral pain perception is produced by traction on mesentery, distention of hollow organs, strong contraction of smooth muscle layers surrounding viscera, ischemia and chemical injury, but is not originated by cutting or burning insults [128].

The vagina, cervix and uterus have both somatic and autonomic innervation via sacral plexus, pelvic ganglia parasympathetic root (pelvic splanchnic nerves), inferior hypogastric plexus, uterovaginal plexus and vaginal nerves. The hypogastric nerve communicates through the sympathetic trunk ganglia with the superior hypogastric plexus and via interganglionic branches and "rami communicantes" up to segments L2 (lumbar) to T10 (thoracic) level of the spinal cord (figure 3).

So innervation of female genitalia is both somatic and visceral, which poses additional difficulty in controlling pain perception.



From Sobotta 2006 in http://clinicalgate.com/female-reproductive-system/

Figure 3 - Innervation of Female Genital tract

2.4 Treatment of Pain [62] [124, 125, 129-133]

Acetominofen or paracetamol (main sever side effect being hepatotoxicity) and Nonsteroidal anti-inflammatory drugs, (NSAIDs) are the first step drugs of choice for pain management and are believed to be analgesic by inhibiting prostaglandin formation (not demonstrated for paracetamol). NSAIDs inhibit Cyclooxygenase (COX) 1 or COX2 isoform enzyme activity and side effects include gastrointestinal ulceration (COX1), inhibition of platelet activity (hence anti-aggregating for COX1) or increase action (for COX2) with added risk of thrombosis in the latter.

Opioids have a weak μ or full μ (MOR) opioid agonist receptor activity and block presynaptic reuptake of serotonin and norepinephrine or both. Except for meperidine and codeine they do not exhibit dose related ceiling. Side effects include addiction, respiratory depression, constipation, nausea and vomiting, pruritus, delirium, sedation, allergy, myoclonus and tolerance (necessity of increasing dose for the same effect in long term usage).

Adjuvant agents for pain control may be used and include:

- Alpha (α) -2 adrenergic agonists (clonidine, tizanidine) have anti- nociceptive spinal activity. Administration can be oral, transdermal or epidural.
- Anticonvulsants (gabapentinoids). They suppress action potential generation in hyper-excitable neurons and are used normally in neuropathic pain.
- Antidepressants: Serotonin-norepinephrine reuptake inhibitors (SNRI) and tricyclic antidepressants (TAD). These drugs have multiple actions including previously mentioned reuptake, but also antihistaminic effect, antagonism of adrenergic α1 receptors, antagonism at muscarinic receptors and voltage-gated sodium channels. Also used normally in neuropathic and chronic pain syndromes, helping in management with lower doses of opioids.
- Bisphosphonates are used in metastatic bone pain unresponsive to analgesia alone.
- Calcitonin may be used in osteoporosis related pain
- Corticosteroids may be useful when inflammatory pain is present
- Topical analgesics (patch) are frequently used for chronic pain [124, 125, 129] .
- Local anesthetics (lidocaine, ropivacaine, mepivacaine, bupivacaine) are frequently used for acute pain to perform nerve blocking [130, 131] and may be suitable for minor surgery, local excisions and biopsies and are useful in office procedures. Associated side effects include allergic reaction, irritation at the site of injection and local anesthetic systemic toxicity (LAST) with cardiomyopathy [132].
- Metoclopramide, a dopamine agonist, can be used intravenously in acute migraine as adjuvant; it may not relieve pain by itself but it significantly reduces the need for rescue drugs [133].

- **Treatment of Pain (stepwise)**

Table III

World Health Organization (WHO) stepwise treatment of pain

Drugs	Mild Pain	Moderate Pain	Severe Pain
Non opioids	Acetominofen NSAIDs	May associate with 	May associate with
Weak opioids		Codeine or Tramadol (also has weak μ agonist activity)	
Strong opioid (full μ agonist activity)			Morphine Other opioids (meperidine, methadone, buprenorphine, etc.)
	Step 1	Step 2	Step 3

2.5 Pain in Office Hysteroscopy [62, 67-72, 96]

Pain in office hysteroscopy still poses a problem [62, 67-73, 96] as seen in Table IV. Even the most optimistic authors who advocate office hysteroscopy and surgery without analgesia or anaesthesia have yet to establish an adequate strategy for painless procedures and we think there is room for investigating new approaches which might influence patient's acceptance of office hysteroscopy.

The original technique of hysteroscopy (and still is performed by many practitioners) involves the use of a vaginal speculum, traction upon the cervix with a tenaculum and, if needed, dilatation of cervical canal with Hegar dilators and finally the introduction of the hysteroscope. It has been established by several authors that a "no touch vaginoscopic approach" is less painful than traditional speculum introduction and tenaculum traction [61, 63, 64, 66, 90, 134]. Guida in 2006 also established, using pain score evaluation at each phase of the procedure, that the most painful step of hysteroscopy was the progression through the cervical canal up and through the internal orifice (phase II of his randomized controlled trial) [63]. So, even if we eliminate speculum insertion and vulsellum grip, progression of the hysteroscope through the cervical canal will still cause discomfort by stretching of its smooth muscular layer walls, especially when traversing the upper (inner) sphincter.

2.6 Frequency of pain in Hysteroscopy

Evaluation of frequency varies with population, methodology of pain assessment and author. As shown in table IV, there seems to be a non-negligible percentage of patients for whom the procedure is quite uncomfortable.

Table IV

Pain evaluation during hysteroscopy

	Scope size	*Moderate*	*Severe*
De Angelis	Traditional Hysteroscopy Mini Hysteroscopy	57% 21%	14% 2%
Bettocchi (Surgery)	Mini Hysteroscopy	5% to 26%	No record
Campo	Traditional Hysteroscopy Mini Hysteroscopy	Mean VAS 2.8 Mean VAS 1.8	No record
Van den Bosch	Endometrial biopsy Mini Hysteroscopy	Median 5.1 Median 2.7	No record
Diniz	Traditional Hysteroscopy Mini Hysteroscopy	32% 32%	41.4% 20.3%
Paulo 2015 Systematic Review	Mini Hysteroscopy Mini hysteroscopy	30% (VAS $\geq$ 4) 13% (VAS $\geq$ 5)	

PART II – RESEARCH

1. Goals of Research

1) To evaluate if pain perception can be reduced by decreasing the hysterocope diameter

2) To determine the proportion of women who will still complain of discomfort with smaller endoscopes

3) To assess whether other clinical factors may influence pain perception in office hysteroscopy

4) To determine if psychological profile of women can influence pain and if satisfaction questionnaires correlate well with pain

5) To evaluate if the new anaesthetic approach can effectively reduce discomfort in Office Hysteroscopy

6) To suggest future work in order to elaborate guidelines and strategies for pain evaluation in real time and reduce the distress associated with hysteroscopy

For each of these objectives an investigation was conducted. Five papers were published with interesting conclusions. Results will be discussed and future perspectives set forth and suggested.

2. Materials and methods

1) Our first paper "Is pain better tolerated with mini-hysteroscopy than with conventional *device? A systematic review and meta-analysis"*, was processed according to the protocol registration http://www.crd.york.ac.uk/PROSPERO/ CRD42014010672.
Studies were sought with key words "hysteroscopy" and "pain" from the following sources: Pubmed/ Medline (465), Portal de Pesquisa da BVS (214), LILACS (13) CINHAL, Embase and Cochrane database (82) Cochrane systematic reviews (3) DARE systematic reviews (4) IBECS (3) Scielo (8) Global Health Library (GHL), (20) Western Pacific region Health Index (WPRIM) (12) Index Medicus for the Eastern Mediterranean Region (IMEMR) (8) and Index Medicus for South-East Asia Region (IMSEAR) (1) giving a total 834 hits. Time frame was from 2000 onward. After reading titles and eliminating duplicates, 94 abstracts were independently assessed by three authors (A.P., M. S. and C.P.) and of theses, 33 articles retrieved for detailed analysis. Seven high quality papers from Randomized Controlled Trials (RCT) which included eight studies involving a total of twenty three hundred and twenty two women were selected from literature sources. RevMan 5.0 (a standard meta-analysis software) was used and we computed standardized mean differences also known as Cohen' d and 95% confidence intervals (CI) for all studies. Heterogeneity was tested using the Q statistic and the I^2 statistic and we assessed for bias using the Cochrane tool for bias assessment.
2) Our second paper *"What proportion of women refer moderate to severe pain during Office Hysteroscopy with a mini-hysteroscope? A systematic review and meta-analysis"* was also processed in accordance to the protocol registration http://www.crd.york.ac.uk/PROSPERO/CRD42014010557.
Studies were sought with key words "hysteroscopy" and "pain" from 2000 to December 2014 from the following sources: Pubmed/ Medline, CINHAL, Embase and Cochrane database, Cochrane systematic reviews, Portal de Pesquisa da BVS, LILACS, DARE systematic reviews, IBECS, Scielo, Global Health Library (GHL), Western Pacific region Health Index (WPRIM) Index Medicus for the Eastern Mediterranean Region (IMEMR) and Index Medicus for South-East Asia Region (IMSEAR), giving a total 863 hits. After reading titles and eliminating duplicates, 94 abstracts were independently assessed by four authors (A.P., M. S., C.P. and V.A.) and of these, 35 articles retrieved for detailed analysis involving a total of seventeen hundred and sixty one women were included and analyzed. Letters requesting data lacking were sent to authors in an attempt to complete the study with as much data as possible. It was impossible to retrieve original data in ten, four were reviews and in the remainder, various medications or other interventions were associated with hysteroscopy and so were considered by revision authors to potentially alter results. MetaXL 1.0. (EpiGear International Pty Ltd, Wilston, Queensland, Australia) was used to pool individual prevalence from each study. We reported the estimated prevalence for all studies and by two subgroups: (i) RCT and (ii) Prospective Trials (PT) reporting prevalence with 95% confidence intervals. Due to significant heterogeneity between studies, we estimated the pooled prevalence for each group using the random-effects model.
3) Our third paper was based on a Prospective Cohort Observational Trial (PT) registered at ClinicalTrials.gov Protocol and Results Registration System NCT02543515 under the general name "*Psychosocial and Clinical Characteristics Predicting Women's Acceptance of Office Hysteroscopy*. This trial was the basis for three papers following analyzes of data extracted from our database enrolling one hundred and eighteen patients scheduled for Office Hysteroscopy (OH) at Centro Hospitalar Tondela-Viseu, Portugal. One hundred cases were included and statistical analysis for *"Hysteroscopy and pain: what risk factors should we consider in office hysteroscopy? are there really any?"* was performed with SPSS 22.0 IBM for windows and in a statistical hypothesis

test with a p value < 0.05 the effect was considered significant so confidence intervals are reported with 95% assurance level. We conducted multivariate ordered logistic regression analysis exploring the effect of menopause, dysmenorrhea and history of menorrhagia, parity of women, previous cervical surgery and age in pain score.

4) Our fourth article *"Pain, anxiety and patient satisfaction in office hysteroscopy, is there a link? Are patient satisfaction questionnaires reliable?"* was written on results from the same Trial nº NCT02543515 registered at ClinicalTrials.gov Protocol and Results Registration System. One hundred women scheduled for Office Hysteroscopy were included and analyzed. Analysis was performed with SPSS 22.0 IBM for windows and in a statistical hypothesis test with a p value < 0.05 the effect was considered significant. The confidence intervals are consequently reported with a 95% assurance level. The normal goodness of fit testing was applied for all quantitative variables. Kolmogorov-Smirnov test revealed that for almost all quantitative variables the normal distribution fit is rejected. In accordance we performed non parametric statistical tests. Kruskal Wallis test was used to evaluate the association between the pain score and the satisfaction variables, Spearman's correlation was used to correlate anxiety and pain, and finally Receiver Operating Characteristic (ROC) were constructed with answers from satisfaction questionnaires in order to establish cutoff points.
5) For our fifth article *"Office Hysteroscopy and pain control, a multicenter study comparing pain by scope size. Introducing the novel "hysteroscopic anaesthesia" technique"* we invited the Department of Gynaecology of Hospital das Forças Armadas Lisboa, Portugal who contributed with eighty one women scheduled for OH for a multicenter prospective observational study. The Department of Obstetrics and Gynecology of Centro Hospitalar Tondela-Viseu, Portugal enrolled one hundred women. Protocols' had slight differences in scope size (3.5mm at Viseu versus 5mm at Lisboa), use of an innovating local anaesthesia in Lisboa and pain score evaluation which was Visual Analogue Scale (VAS) scoring in Viseu and a Numeric Rating Scale (NRC) in Lisboa. Statistical analysis was performed with SPSS 22.0 IBM for windows and in a statistical hypothesis test with a p value < 0.05 the effect was considered significant.

3. Results and findings

Paper number one: *"Is pain better tolerated with mini-hysteroscopy than with conventional device? A systematic review and meta-analysis",* was processed according to the protocol registration http://www.crd.york.ac.uk/PROSPERO/ CRD42014010672.

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REVIEW

Is pain better tolerated with mini-hysteroscopy than with conventional device? A systematic review and meta-analysis

Hysteroscopy scope size and pain

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Abstract
Background Hysteroscopy is an indispensable approach in gynecology. Miniaturization may reduce pain allowing office procedures without anesthesia.
Objectives Our main objective is to determine if modifications in scope diameters have made office hysteroscopy less painful.
Search strategy Studies were sought with key words "hysteroscopy" and "pain" from available online sources. Time frame was from 2000 onward. Thirty-three articles were retrieved for detailed analysis.
Selection criteria Prospective randomized trials, studying pain as main outcome in office hysteroscopy expressed in means, confidence intervals and SD, comparing office mini-hysteroscopy to conventional hysteroscopy. Studies or arms within a study where conscientious sedation, anesthesia or non-steroidal drugs were used were excluded.
Data collection and analysis We analyzed data from eight studies (seven RCT) comparing mini-hysteroscopy with conventional scopes, involving a total of twenty-three hundred and twenty-two participants, of which nineteen hundred and eighty-six completed the intervention.
Main results A meta-analysis revealed a significant reduction pain score (MD: −3.64; 95 % CI −5.16 to −2.12; test for overall effect $p < 0.00001$) and available data support miniaturization decreases pain in outpatient hysteroscopy.
Conclusions Pain in office hysteroscopy is lower with mini-hysteroscopes.

Keywords Hysteroscopy · Scope size · Pain

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Introduction

Hysteroscopy is a routine technique allowing direct visualization of unsuspected pathology: endometrial hyperplasia, cancer, and other conditions and is considered gold standard in uterine abnormal bleeding. It allows histological sampling cancer staging and foreign bodies can be retracted or inserted into cavity and tubes. Hysteroscopy is useful in infertile women.

Modern mini-hysteroscopes avoid cervical dilation, misoprostol facilitates operations [1, 2], either by vaginal or sublingual administration [3], and the vaginoscopic no-touch approach [4–8] improved tolerance as data in a 2010 systematic review by Cooper [8] demonstrate. Reduction in pain has led to performing examination and even operations without anesthesia [2, 9–11]. Ultrasonography and 3D sonohysterography are not as accurate in diagnosing intrauterine abnormalities [12], and hysteroscopy is generally needed to confirm diagnosis. It also plays an important role in fertility treatment workup [13]. Both rigid and flexible mini-hysteroscopes reduce pain and may be adequate for examination [14] but rigid scopes seem to have superior optical properties [15].

Distension media is important. Plain water can be harmful, glycine and sorbitol/mannitol are adequate for mono-polar electrosurgery, but can provoke fatal

outcome. Gas embolization is common, even using normal saline as bipolar electrodes produce bubbles and can be life-threatening. Both CO_2 and normal saline are adequate for diagnostic outpatient hysteroscopy [16] as Cooper's 2010 systematic review on effect on pain concluded, but saline is more convenient if surgery is to be done [17].

Pain is responsible for vasovagal syndrome in 0.21–30 % and leads to halting of procedure. Various interventions [18, 19], medications [20, 21], para-cervical block cocktails, and conscious sedation have been suggested to control pain without convincing results [1, 22–26]. Cengiz [27] compared intrauterine lidocaine and paracervical block and concluded there was no significant difference, but lidocaine has a longer post-operative effect. Two recent systematic reviews in 2010, one by Cooper [24] and another by Ahmad [28] have, however, suggested a reduction of pain with local anesthetic, but "clinical significance of results is limited as the reduction in mean pain score is small" [28]. Success with outpatient technique without anesthesia is associated to very low cost of gynecological care and justifies its generalized use for some authors [5]. Pain perception may vary among population subgroups [29, 30].

A recent paper by Cicinelli [31] summarizes evidence gathered from various studies and sources.

Objectives

Our main objective is to determine if modifications in scope diameters has made office hysteroscopy less painful. While most studies agree that slender hysteroscopes reduce pain, one randomized controlled trial (RCT) from 2005 by Rullo [32] and one prospective cohort study by Torok in 2012 [33] failed to find statistical difference between scope diameters and pain scores. So the question remains: is reduction in hysteroscope diameter associated with lower pain perception?

Search strategy

Studies were sought with key words "hysteroscopy" and "pain" from the following sources: Pubmed/Medline (465), Portal de Pesquisa da BVS (214), LILACS (13) CINHAL, Embase and Cochrane database (82) Cochrane systematic reviews (3) DARE systematic reviews (4) IBECS (3) Scielo (8) Global Health Library (GHL), (20) Western Pacific region Health Index (WPRIM) (12) Index Medicus for the Eastern Mediterranean Region (IMEMR) (8), and Index Medicus for South-East Asia Region (IMSEAR) (1) giving a total 834 hits. Time frame was from 2000 onward. After reading titles and eliminating duplicates, 94 abstracts were independently assessed by three authors (A.P., M. S. and C.P.) and of theses, 33 articles retrieved for detailed analysis.

Methods

Ethical and regulatory compliance: This study was conducted in compliance with the protocol, the Declaration of Helsinki, the Good Epidemiological Practice, and all applicable laws and regulations.

Seven papers (including eight studies) were selected from literature sources. Flow chart of selection is specified in Fig. 1.

Using standard meta-analysis software (RevMan 5.0),[1] we computed mean differences (MD) also known as Cohen' d and 95 % confidence intervals (CI) for all studies. Because we expected considerable heterogeneity, we use a random-effects model taking into account both within and between-study variation to compute the overall effect estimate. However, we first tested the heterogeneity using the Q statistic and the I^2 statistic with values of 0.25, 0.50, and 0.75 indicating low, moderate, and high degrees of heterogeneity. Sensitivity analysis by excluding one study at each turn and pooling results from the remainder further confirms the robustness of our findings. To explore the heterogeneity across studies, we conducted subgroup meta-analyses (by assessing the difference between groups in trials with similar participant characteristics). Publication bias was assessed using funnel plot analysis. Visual inspection of a funnel plot can give an indication of publication bias; the studies can be expected to spread symmetrically about the pooled effect size when publication bias is absent.

Eligibility criteria

Seven RCT [1, 22, 32, 34–37] (giving a total of eight studies) comparing pain during mini-hysteroscopy versus conventional hysteroscopy, involving a total of twenty-three hundred and twenty-two patients were included and analyzed.

Other studies were rejected for the following reasons: De Iaco [38] was to our knowledge the first to publish data on pain and outpatient hysteroscopy, but his work was observational. For the same reason Siristatidis [9], Torok [33], and Cicinelli [30] were also excluded. Bettocchi's studies had different objectives or were operative hysteroscopy as was De Placido's paper [39], and authors judged they were not suitable for the purpose of this study.

[1] Review manager (RevMan) [Computer Program]. Version 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration (2008).

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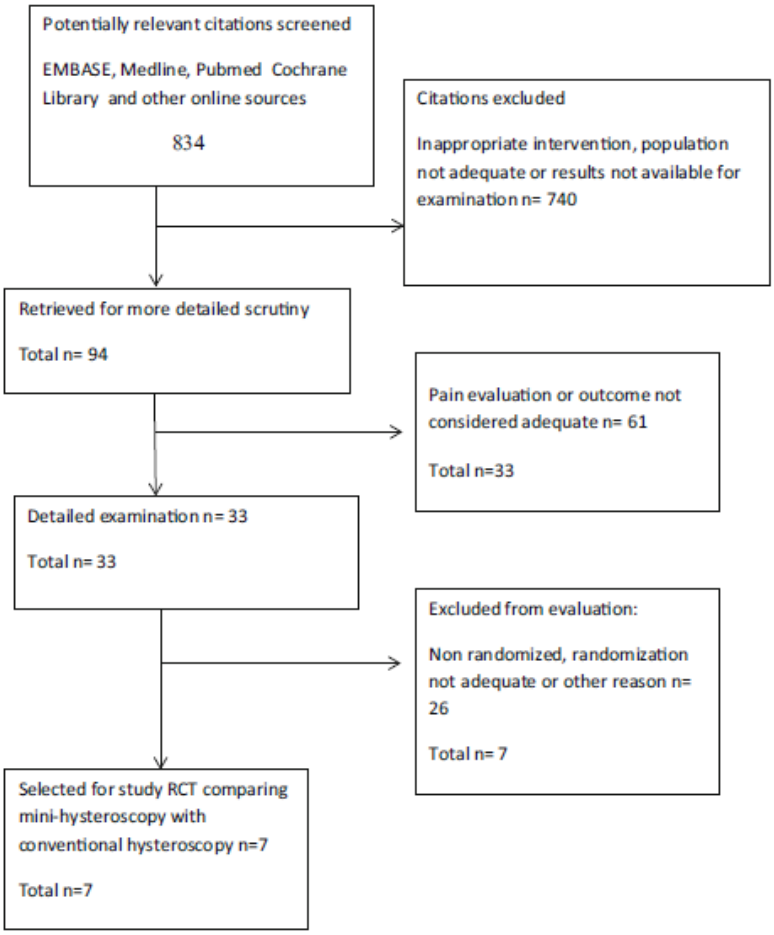

Fig. 1 Flow chart for selection process of studies for evaluation of pain in hysteroscopy

Bias assessment

Our eight studies were assessed for bias using the Cochrane tool for bias assessment. Revision authors judged blinding of personnel in such studies was very unlikely to be effective as operators always knew which hysteroscope is being used. Randomization was judged low risk in seven series and unclear in one, and so was concealment. Blinding of outcome assessors was attained in three and unclear in five. All studies account for missing cases and selective reporting was unclear in one study. Authors believe studies are high quality, having an overall low risk of bias. (Fig. 2).

Results

In order to allow comparison of means and SD results, input was in reference to a 10 cm scale. Other results were converted as described: for Cicinelli's 20 cm scale means variation has a $Y = X/2$ relation with adopted scale. So accordingly $E[Y] = E[Y]/2$ for *means* and $V[Y] = V[X]/4$ for *variance* were taken as comparative values; Kassem reported in absolute numbers and revision authors converted rank classes 1–4 into categories and adapted results to a 0–10 scale, calculating means, variance, and SD for each category.

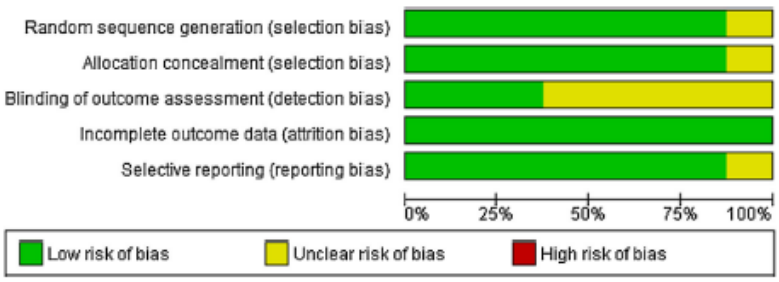

Fig. 2 Risk of bias graph using Cochrane tool for bias assessment: review authors' judgments

Giorda's and Campo's studies seem to have heterogeneity with all others; we doubled check our data extraction but found heterogeneity was high ($I^2 = 99.6$ %, p value <0.001). As a result, we conducted a subgroup meta-analysis (high and low effect studies) and the difference between subgroups effect sizes is significant (the correspondent confidence intervals have no overlapping). Meta-analysis of the eight studies showed a significant reduction in pain scores (MD: −3.64; 95 % CI −5.16 to −2.12; test for overall effect $p < 0.00001$). The implemented subgroup analysis dividing the studies according the effect size strength also showed, for both subgroups, a significant reduction in pain. Fig. 3.

For studies with high effect sizes, the meta-analysis presents MD: −11.26; 95 % CI −12.39 to −10.13 (test for overall effect $p < 0.00001$); for studies with low effect sizes the meta-analysis reveals MD: −1.15; 95 % CI −1.54 to −0.76 (test for overall effect $p < 0.00001$).

Results of sensitivity analysis excluding one by one each study in the analysis at a turn and pooling results from the remainder, further confirmed the robust findings of significant reduction in pain scores as shown in Table 1.

Furthermore, as was expected, Campo and Giorda studies show highest influence in the overall results. Inspection of the funnel plots (subgroup analysis) did not indicate possible publication bias as there seems to be a symmetrical distribution around the means (Fig. 4).

Discussion

Data from all studies suggest mini-hysteroscopy is less painful than conventional hysteroscopy in an office, anesthesia free setting. In the subgroup analysis results, although two studies seem outsiders in respect to others, they go in the same direction and favor reduction of pain with miniaturization. Furthermore, there seems to be no

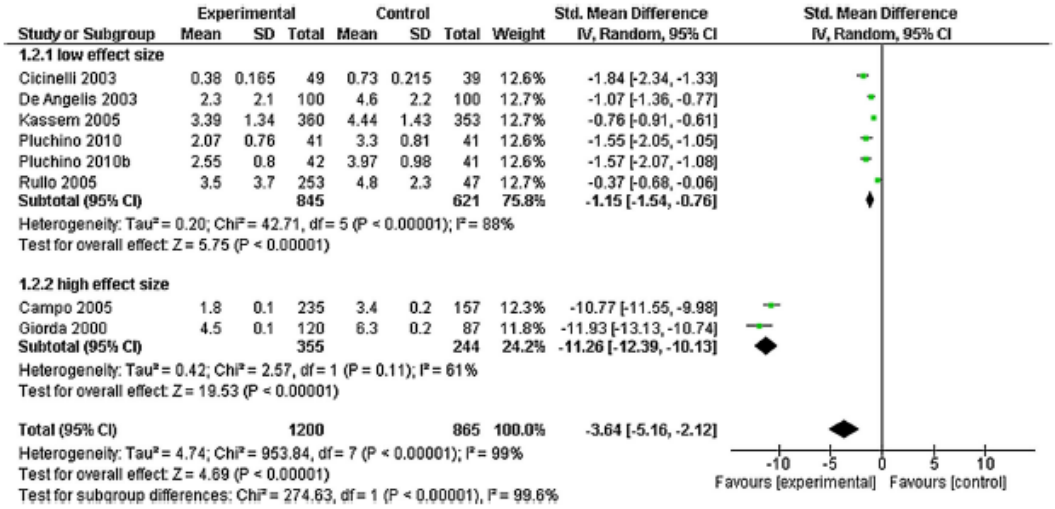

Fig. 3 Forest plot analysis including subgroup results

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Table 1 Sensitivity analysis excluding one study at a time one by one each study in the analysis

Excluded study	Std. mean difference	LCI 95 %	HCI 95 %	I^2
Giorda et al. [36]	−2.51614	−3.85895	−1.17334	99.06196
Pluchino [34] saline	−3.95236	−5.66861	−2.2361	99.36957
Pluchino [34]	−3.94905	−5.66551	−2.23259	99.36937
De Angelis et al. [1]	−4.04133	−5.94324	−2.13943	99.37043
Campo et al. [22]	−2.52677	−3.5681	−1.48545	98.37323
Kassem et al. [37]	−4.10099	−6.2301	−1.97189	99.32171
Rullo et al. [32]	−4.13742	−5.97931	−2.29553	99.35012
Cicinelli et al. [35]	−3.91028	−5.61973	−2.20084	99.36656

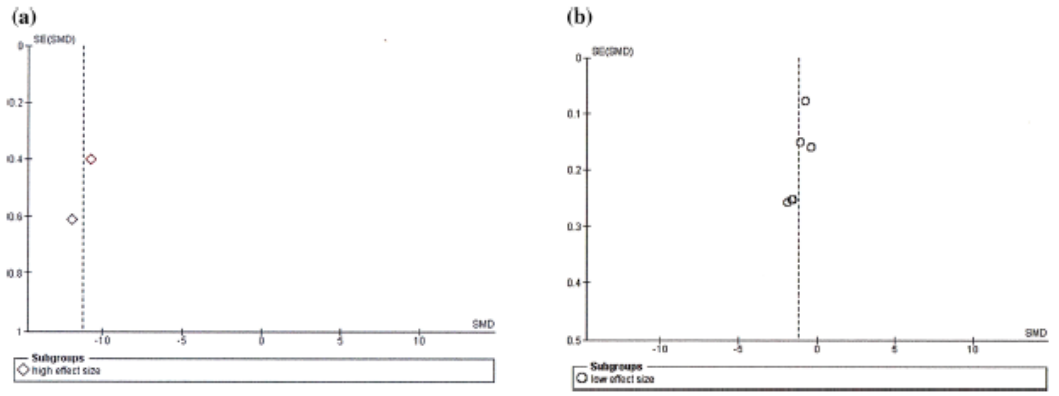

Fig. 4 Funnel plot comparing studies by size effect, **a** subgroup of high effect size values, **b** subgroup of low effect size values

significant differences in quality of vision or diagnostic accuracy with reduction in hysteroscope diameter [1, 11, 22, 32, 34–37].

Not all mini-hysteroscopes used were the same size: 3 mm (Rullo), 3.3 mm (Angelis) and 3.5 mm (Pluchino, Campo, Cicinelli, Giorda and Kassem). Our forest plot does not seem to reflect a difference in pain with these small changes in diameter: the high effect size include two 3.5 mm series (Campo and Giorda), while both smaller diameter hysteroscopy studies (Rullos' 3 mm and Angelis' 3.3 mm) are in line with the other 3.5 mm studies which showed low effect size. We could be tempted to speculate that further reduction in scope diameters might lead to lower pain perception; however, our analysis suggests there may be a cut off around 3.5 mm, below which reduction of scope size might not further reduce pain. Additional studies comparing slender instruments may be warranted to answer this question.

Regarding the inconsistencies found we offer the following possible explanations: Giorda's study was conducted exclusively on postmenopausal women, most likely giving rise to a selection bias; on the other hand in Campo's series, the 5 mm scope arm had to be changed to the mini-hysteroscope in eighty-three cases to complete examination (34 %).

Main findings

Miniaturization of scopes shifts pain levels down, compared to traditional hysteroscopy, allowing accurate gynecological care in an office, anesthetic free environment.

Strengths and limitations

Results showed overall results are very consistent and there seems to be no doubt of a significant reduction of VAS using mini-hysteroscopy. Authors believe that evidence is convincing, accurate, reproducible, and can be extrapolated to general population. For details please refer to Table 2.

Interpretation (findings in light of other evidence)

Miniaturization reduces pain scores and has made hysteroscopy tolerable for most patients.

Table 2 Strength and weakness

	Study type	*n*	Strengths	Weaknesses	Risk of bias
Fluchino et al. [34]	RCT	184	Multicentre randomized trial, several outcome measures including two VAS measures and relating results to medium distention method and operator experience. Patients having additional procedure were not considered in pain evaluation Results were expressed in mean and SE values with 95 % confidence intervals	Population exclusively referred for primary infertility; several outcome measures including two VAS measures and quality of visualization	Authors judged adequate to consider two groups (saline solution or CO_2 as distention media), hence accepting two series for meta-analysis comparison. VAS1 score (immediately after hysteroscopy) was chosen. For this purpose study was considered having low risk of bias with adequate randomization and concealing
De Angelis et al. [1]	RCT	207	Randomized trial at a Obstetrics and Gynecology Department of a University Hospital. Population with various indications for hysteroscopy. Main outcome measure was VAS score Results were expressed in mean and SE values with 95 % confidence intervals	Outcome measures included two VAS scores (immediately after and five minutes after). All patients underwent hysteroscopy with speculum insertion, although no traction or cervical dilatation was allowed	Authors judged adequate to consider this study (using CO_2 as distention media on both arms), accepting series for meta-analysis comparison. VAS score (immediately after hysteroscopy) was chosen. For this purpose study was considered having low risk of bias with adequate randomization and concealing
Campo et al. [22]	RCT	480	Multicentre randomized trial, with main outcome measures of VAS measure, relating results to vaginal delivery or no vaginal delivery and operator's experience. Population with various indications for hysteroscopy Results were expressed in mean and SE values with 95 % confidence intervals	Other outcome measures included quality of visualization. Interchangeability of scopes was allowed. All patients underwent hysteroscopy with speculum insertion, although no traction or cervical dilatation was allowed	Authors judged adequate to consider this study (using saline as distention media on both arms), accepting series for meta-analysis comparison. VAS score (immediately after hysteroscopy) was chosen. For this purpose study was considered *having unclear risk* of bias as interchangeability of scopes was significant and could affect results. Study had adequate randomization and concealing
Kassem et al. [37]	RCT	740	Randomized trial at a Obstetrics and Gynecology Department of a University Hospital. Significant number of participants	Results were expressed in four ranks of pain and in absolute numbers. Revision authors converted ranks into categories and calculated means, variance, SE and 95 % confidence intervals in reference to a 0 to 10 scale to allow comparison	Considering total number of patients involved, revision authors judged adequate to include this study, accepting series for meta-analysis comparison. Randomization was computer generated but concealment was probably not adequate. For purpose of this research study was considered having *unclear risk* of bias
Rullo et al. [32]	RCT	371	Randomized trial at a Obstetrics and Gynecology Department of a University Hospital. Population with various indications for hysteroscopy. Results were expressed in mean and SE values with 95 % confidence intervals	Non equal randomization: smaller number of patients in 5 mm arm Outcome included failure of procedure due to pain (ranging from 3.8 % to 15.4 %.), three evaluations of VAS score at different time (during, immediately after and 30 min after. Diagnostic accuracy and time consumed were also evaluated comparing parity, menopause and scope diameter. All patients underwent hysteroscopy with speculum insertion	Results were expressed in mean and SE values with 95 % confidence intervals (data collected from Cicinelli, E. in his review 2010). For this purpose study was considered *having unclear risk* of bias as neither randomization nor concealment seem to be adequate

Table 2 continued

	Study type	*n*	Strengths	Weaknesses	Risk of bias
Cicinelli et al. [35]	RCT	100	Randomized trial at a Obstetrics and Gynecology Department of a University Hospital. All patients were referred for abnormal uterine bleeding. The vaginoscopic "no touch" approach was used to minimize pain Results were expressed in mean and SE values with 95 % confidence intervals	Evaluation of pain used a 20 cm ruler and prior to examination a "pain expectancy" form was completed by each patient (could subjectively influence rating of actual pain experienced) Pain evaluation was done by placing a mark on the ruler	Authors judged adequate to consider this study (using saline as distention media on both arms), accepting series for meta-analysis comparison. VAS score (immediately after hysteroscopy) was chosen. For this purpose study was considered *low risk* of bias although it is not clear suggestion from prior expectancy rating could affect results. Study had adequate randomization and concealing
Giorda et al. [36]	RCT	240	Randomized trial at a Obstetrics and Gynecology Department of a University Hospital. 4 Results were expressed in mean and SE values with 95 % confidence intervals	Computer randomization, but not blind study. Included 3 groups: 3.5 mm scope, 5 mm scope and 5 mm scope with paracervical block Population referred was exclusively post-menopausal	Authors judged adequate to consider two study arms: 3.5 mm scope and 5 mm scope without paracervical block. N = 240 (using CO_2 as distention media on both arms), accepting series for meta-analysis comparison. VAS score (immediately after hysteroscopy) was chosen Although not blind, authors were satisfied for the purpose of this study allocation was computer randomized and judged low risk for bias

Conclusions

From the evidence gathered, we must conclude that mini-hysteroscopy is the most acceptable and suitable for office in outpatients. Traditional hysteroscopy (5 mm scopes) may not be the most adequate for this purpose.

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Conflict of interest The authors have no conflict of interest with any institution private or public.

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Paper number two: "*What proportion of women refer moderate to severe pain during Office Hysteroscopy with a mini-hysteroscope? A systematic review and meta-analysis*" was also processed in accordance to the protocol registration http://www.crd.york.ac.uk/PROSPERO/CRD42014010557

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REVIEW

What proportion of women refers moderate to severe pain during office hysteroscopy with a mini-hysteroscope? A systematic review and meta-analysis

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Abstract
Background Mini-hysteroscopy is believed to be pain-free or in the least bearable. Office procedures are therefore usually performed without analgesia or anesthesia. Is it indeed as tolerable as papers and authors suggest?
Objectives To estimate what proportion of women reports moderate to severe discomfort during examination using the smaller diameter scopes.
Search strategy Online sources were search with key words "hysteroscopy" and "pain" from 2000 to December 2014. Thirty-five articles were retrieved for detailed analysis.
Selection criteria Randomized controlled trials (RCT) and well-designed prospective trials (PT) studying pain as main outcome, in office mini-hysteroscopy in at least one arm. Studies or arms within a study where conscientious sedation, anesthesia, or non-steroidal drugs were used were excluded. Chosen data collected was the number of women referring moderate to severe pain compared to total women with intervention in the arm or study. Authors were contacted to try to retrieve unpublished data for analysis.
Data collection and analysis We performed a meta-analysis from eight studies (six RCT and two PT) comparing pain reported as moderate or severe to total women in mini-hysteroscopy.
Main results A meta-analysis estimated the pooled prevalence of pain (>3–10 on 10 cm visual analog scale) for all studies and by two subgroups: (1) RCT and (2) PT. Due to significant heterogeneity between studies, we used the random effects model. Results revealed a high prevalence of pain in outpatient mini-hysteroscopy.
Conclusions Office mini-hysteroscopy is painful.

Keywords Hysteroscopy · Pain · Office hysteroscopy · Mini-hysteroscopy

Introduction

Outpatient hysteroscopy technique has a very low cost and reduction in pain, has led to performing examination and even operations without anesthesia [1–4], justifying its generalized use in gynecological care [5]. It is very accurate for diagnosis of endometrial cancer, polyps, and miomas [6].

The use of mini-hysteroscopes (outer sheet diameter from 3 to 3.7 mm) avoiding cervical dilation, together with cervical ripening with misoprostol, facilitates operation and improves tolerance [1, 5, 7–14]. Both rigid and flexible mini-hysteroscopes reduce pain and may be adequate for examination [15], but rigid scopes have better optical properties [16].

A recent systematic review and meta-analysis comparing scope diameter and pain has reached the conclusion

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that mini-hysteroscopes versus conventional 5 mm devices significantly lower pain levels; it also suggests that there may be a cut-off point of around 3.5 mm below which further reduction in scope size may not additionally reduce discomfort [17].

Cooper's data in a 2010 systematic review [11] demonstrated that the vaginoscopic approach also reduced suffering. Another systematic review by Cooper concluded that both CO2 and normal saline are adequate as distension media for diagnostic outpatient hysteroscopy [18].

Various interventions [19, 20] and medications have not reduced pain [7, 21–27]. New data on two recent systematic reviews in 2010, one by Ahmad [28] and another by Cooper [23] have suggested pain can be reduced with the use of local anesthetic.

Perception of pain may vary among population subgroups [29, 30] and evaluation of intensity may be done with various tools, most commonly 10 cm visual analog scale (VAS) and numeric rating scale (NRS) [31–34]. Pain rating according to a 0–10 cm VAS (0 = no pain, 1–3 mild pain, 4–7 moderate pain, 8–10 severe pain) is used by various authors [7, 32, 33, 35] and is recommended by World Health Organization [36] and Vancouver Island Health Authority [37]. Jensen recommends moderate pain be considered only above 4.4 cm on a 10 cm scale [38].

There is a difference between somatic and visceral pain: the latter is perceived more diffusely with marked autonomic phenomena including pallor, profuse sweating, nausea, gastrointestinal disturbances, and changes in body temperature, blood pressure, and heart rate [39, 40]. Hystersocopists are familiar with these complications as vasovagal syndrome occurs in 0.21–30 % of examinations [41, 42].

Objectives

Our main objective is to determine, when using less painful mini-hysteroscopy [7, 17, 21, 43], what proportion of women experiences moderate to severe pain and prove it is either painless, or on the contrary, an uncomfortable experience.

Search strategy

Studies were sought with key words "hysteroscopy" and "pain" from 2000 to December 2014 from the following sources: Pubmed/Medline, CINHAL, Embase and Cochrane database, Cochrane systematic reviews, Portal de Pesquisa da BVS, LILACS, DARE systematic reviews, IBECS, Scielo, Global Health Library (GHL), Western Pacific region Health Index (WPRIM) Index Medicus for the Eastern Mediterranean Region (IMEMR), and Index Medicus for South-East Asia Region (IMSEAR), giving a total 863 hits. After reading titles and eliminating duplicates, 94 abstracts were independently assessed by four authors (A.P., M. S., C.P. and V.A.) and of these 35 articles retrieved for detailed analysis.

Methods

Ethical and regulatory compliance: this study was conducted in compliance with the protocol, the Declaration of Helsinki, the Good Epidemiological Practice, and all applicable laws and regulations.

Eight papers were selected from literature sources. Flow chart of selection is specified in Fig. 1. After initial selection, ninety-four papers were scrutinized. Fifty-nine were rejected for inadequate pain outcome assessment. Of the remaining thirty-five, it was impossible to retrieve original data in ten, four were reviews and in the remainder, various medications or other interventions were associated with hysteroscopy and so were considered by revision authors to potentially alter results.

In our main analysis, we took into account VAS greater than three as indicative of moderate pain, which in practice means authors scores on VAS was at least four in ten (as centimeters rather than millimeters are commonly used). Nevertheless we included a second analysis considering VAS greater than five on a 10 cm scale to satisfy stricter criteria [38].

MetaXL 1.0., a tool for meta-analysis in Microsoft Excel, was used to pool individual prevalence from each study. We reported the estimated prevalence for all studies and by two subgroups: (1) RCT and (2) PT reporting prevalence with 95 % confidence intervals. Due to significant heterogeneity between studies, we estimated the pooled prevalence for each group using the random effects model. Forest plots are used to present the meta-analysis results.

Eligibility criteria

Six RCT [7, 21, 27, 44–46] and two prospective studies [47, 48] evaluating pain during mini-hysteroscopy and involving a total of seventeen hundred and sixty-one women were included and analyzed (Table 1).

Other studies where hysteroscopy was used [1, 8, 10, 16, 25, 26, 29, 43, 49, 50] were rejected for insufficient data (although several contacts were made to retrieve them), did not adequately score pain [30, 51], used a conventional 5 mm scope [9, 19, 20, 52–54], included local anesthesia [15, 23, 24, 28], hysteroscopic surgery [2] or other intervention was associated [5, 11, 18, 55], and revision authors judged they were not suitable for the purpose of this study.

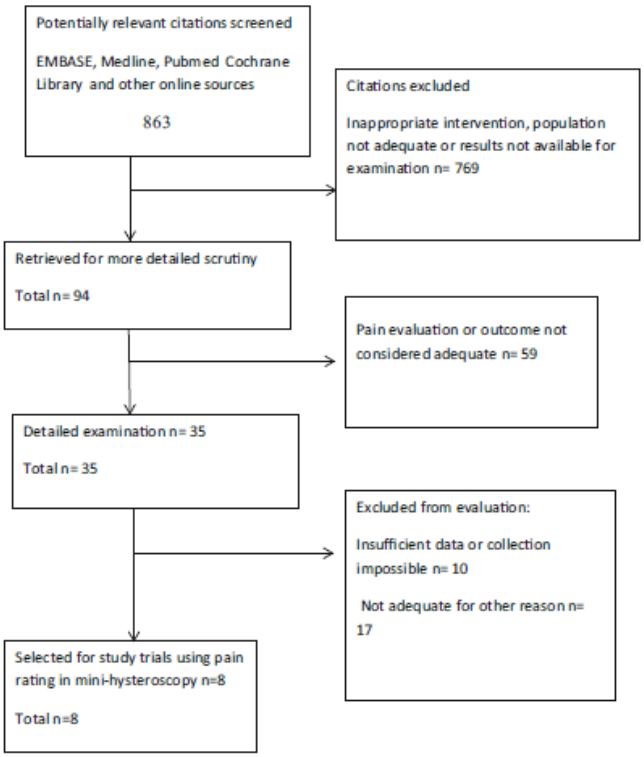
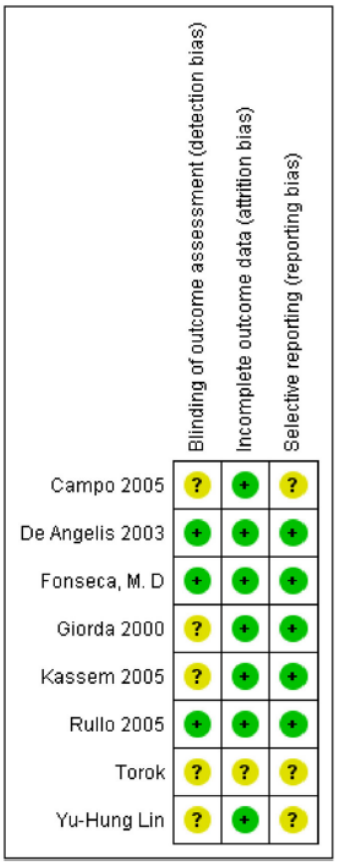


Fig. 1 Flow chart for selection process of studies for evaluation of pain in hysteroscopy

Table 1 Hysteroscopy 3–3.7 mm scope results—chosen arm in italics

References	Type	*N* total	Arms—scope diameter	*N* (VAS score 4–10)	How data were collected
De Angelis et al. [7]	RCT	*102*	*3.3 mm*	23	*Moderate plus severe*
			5 mm		
Campo et al. [21]	RCT	*240*	*3.5 mm*	32	*Failure rate*
			5 mm		
Kassem [44]	RCT	*346*	*3.5 mm*	27	*Painful and very painful*
			5 mm		
Rullo et al [45]	RCT	*310*	*3 mm*	27	*Only intolerable*
			5 mm		
Giorda et al. [46]	RCT	*121*	3.5 mm	106	*Data from author*
			5 mm		
			5 mm + cervical block		
Yu-Hung Lin et al. [27]	RCT	*84*	*3.1 mm flexible*	44	*Data from author*
			3.1 mm flexible + buprenorphine		
De Freitas Fonseca et al. [47]	Prospective	*558*	*3.5 mm*	180	*Only intolerable (VRT >7)*
Torok and Major [48]	Prospective	*41*	*Diagnostic 3.7 mm*	17	*Data from author*
			Operative 5.5 mm		

Table 2 Mini-hysteroscopy Bias assessment



Bias assessment

Our eight studies were assessed for bias using the Cochrane tool for bias assessment. Revision authors judged that blinding of personnel in such studies was very unlikely to be effective as was randomization and sequence allocation concealment. Revision authors also judged that even if present, theses bias might not significantly influence results. Blinding of outcome assessment, completion of data, and selective reporting were taken into account. Authors believe studies to have an overall low risk of bias (Table 2).

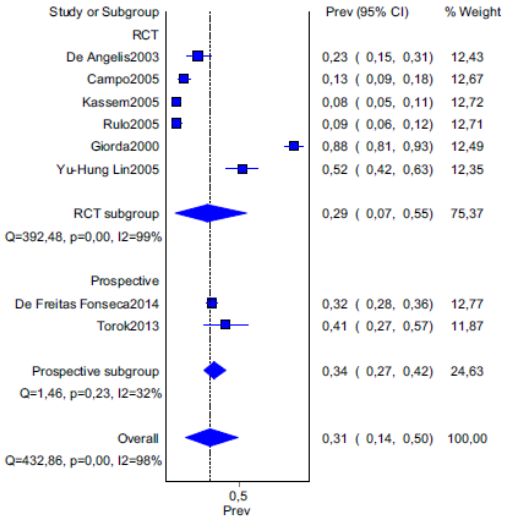


Fig. 2 Forest plot VAS 4 or greater by subgroups (RCT and Prospective) using random effect model

Results

Due to significant heterogeneity between studies (see Cochran's Q and I^2 observed results in Fig. 2), we estimated the pooled prevalence using a random effects model for meta-analysis. To allow secondary scrutiny, a subgroup analysis was performed, and the estimated prevalence for studies was reported in two subgroups: (1) RCT and (2) PT. The estimated prevalence in RCT subgroup is 29 % (95 % CI 0.07–0.55) and the estimated prevalence of PT subgroup is 34 % (95 % CI 0.27–0.42). The overall estimated prevalence is 31 % as shown in Fig. 2 (95 % CI 0.14–0.50).

Quite surprisingly, a high prevalence of moderate to severe pain in both in RCT and in PT was found. It is similar in both groups and the overall results point to around thirty-one percent of women referring appreciable discomfort (Fig. 2). There is no significant difference between pain prevalence of both subgroup results, since the confidence intervals overlap.

As shown in Table 3, further sensitivity analysis on our first analysis, excluding each study one by one in the analysis at a turn and pools results from the remainder, additionally confirmed the robust findings of no significant differences in pain prevalence.

Table 3 Sensitivity analysis

References	Pooled Prev	LCI 95 %	HCI 95 %	I 2	I 2 LCI 95 %	I 2 HCI 95 %
De Angelis et al. [7]	0.32	0.13	0.54	98.61	98.09	98.99
Campo et al. [21]	0.34	0.14	0.56	98.55	97.99	98.95
Kassem [44]	0.35	0.16	0.57	98.28	97.57	98.78
Rullo et al. [45]	0.35	0.16	0.57	98.38	97.72	98.84
Giorda et al. [46]	0.23	0.12	0.36	96.63	94.83	97.80
Yu-Hung Lin et al. [27]	0.28	0.11	0.48	98.50	97.92	98.92
De Freitas Fonseca et al. [47]	0.30	0.10	0.55	98.51	97.93	98.93
Torok and Major [48]	0.29	0.12	0.50	98.59	98.06	98.98

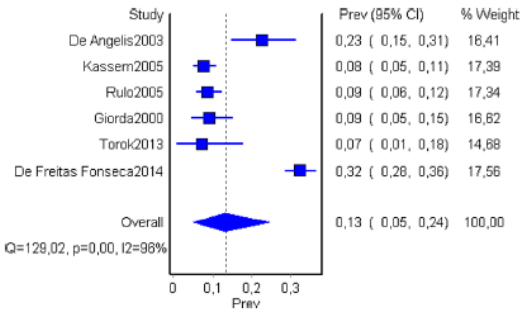


Fig. 3 Forest plot for VAS 5 or greater

Even when taking into account Jensen's definition of moderate pain, (we used VAS greater than 5, well above his proposed threshold of 4.4 mm) prevalence of pain is still surprisingly high for such a strict limit, giving an overall non-negligible value of 13 % (95 CI 0.05–0.24) Fig. 3.

Discussion

To the best of our knowledge this is the first paper focusing on prevalence of pain in hysteroscopy, contrary to most studies which compare pain reduction in various modifications of technique and scope size.

Office hysteroscopy (OH) has been a revolution in gynecological care as Sardo [56] has evidenced in his 2010 review of office based procedures. There seems to be no doubt that OH surgery is feasible, quick, and cost efficient. In this series of studies, the focus is on success rate, patient discomfort, and complication rate. Various regiments of oral, intramuscular, and intravenous medication are used, along with sedation and local anesthesia, which do not simplify evaluation of pain and discomfort. However, pain is not a primary outcome measure and in five out of eighteen studies it is not even evaluated. Furthermore in the tubal ligation studies, two out of nine used VAS, four stated discomfort or tolerance arbitrarily as "good or excellent" or "satisfied/very satisfied," "highly satisfied" and "painless/scarcely painful."

Angioni [57] had already established the usefulness of OH in diagnosis of abnormal uterine bleeding conditions with an overall excellent sensitivity and specificity having advantage over blind biopsy (Novak's currete and D&C). He did not evaluate pain simply stating "It can be performed with little or no cervical dilatation and anesthesia is generally not required"; he also stated "the cost is approximately one tenth of a Hospital D&C."

Our aim was not to prove such or such modification reduces pain perception, but to try to quantify actual suffering of patients undergoing hysteroscopy.

Iaco in 2000 wrote "In this study, diagnostic hysteroscopy was painful even with experienced operators using atraumatic technique; one-third of women experienced severe pain, although most (83 %) claimed they were willing to have a repeat procedure under the same conditions." [52] We would argue that, given no other option, patients are willing to accept a great deal of suffering in order to be treated or in fear of having a serious life-threatening condition.

Data suggest mini-hysteroscopy in an office anesthesia-free setting is probably more painful than previously thought. In the subgroup analysis, results are similar and sensitivity analysis shows robust findings.

Regarding results, we believe they may underscore actual pain for a number of reasons: Giorda [46], Yu-Hung Lin [27] and Torok [48] were the only results actually confirmed by authors' reply. De Angelis figures were calculated from percentage published in the paper and should reflect his original data. Kassems [44] absolute numbers refer to a four digit verbal score, which for comparative reasons was converted into a 10 cm scale, corresponding to interval shown in brackets for each class: no pain (0–2.5), discomfort (>2.5–5), pain (>5–7.5), and very painful (> 7.5–10). We used his data from pain and very painful groups, which would correspond to VAS >5. Fonseca's [47] results are described in Verbal Rating Scale (VRS)

Table 4 Studies considered for analysis

References	Type	*N* total	Arms	N (VAS score 4–10)	How data were collected
De Angelis et al. [7]	RCT	102	*3.3 mm*	23	Moderate plus severe (in text)
			5 mm		Not used
Campo et al. [21]	RCT	240	*3.5 mm*	32	Failure rate (in text)
			5 mm		Not used
Kassem [44]	RCT	346	*3.5 mm*	27	Painful and very painful (in text)
			5 mm		Not used
Rullo et al. [45]	RCT	310	*3 mm*	27	only intolerable (in text)
			5 mm		Not used
Giorda et al. [46]	RCT	121	*3.5 mm*	106	data from author :Giorda
					DATA of Discomfort perceived on a 10 grade visual analog scale (1 mild to 10 intolerable)
					121 patients enrolled in the Narrow sheath hysteroscope
					Data lacking for 1 patient
					Tolerance from 1 to 3 = 14 patients
					Tolerance from 4 to 6 = 95 patients
					Tolerance >6 = 11 patients
			5 mm		Not used
			5 mm + cervical block		Not used
Yu-Hung Lin et al. [27]	RCT	*84*	*3.1 mm flexible*	*44*	Data from author:
					Dear Dr: Paulo:
					The following is the information you need:
					Moderat: 44, severe: 0
					But I want to remind you that I used Olympus flexible hysteroscope.
			3.1 mm flexible + buprenorphine		Not used
De Freitas Fonseca et al. [47]	Prospective	*558*	*3.5 mm*	*180*	only intolerable (VRT > 7) (in text)
Torok and Major [48]	Prospective	*41*	*Diagnostic 3.7 mm*	17	Data from author: Diagnostic (3.7 mm)
					VAS 0-3 VAS 4–10
					Sterility (n = 20) 11 9
					Parous (n = 11) 7 4
					Menopause (n = 10) 6 4
			Operative 5.5 mm		Not used
Excluded studies					
Guida et al. [1]	RCT		3.5 mm		Email sent 13-08-2014. No answer from author
			5 mm		
Sagiv et al. [8]	RCT		3.7 mm vaginoscopic		Email sent 13-08-2014 15:32 Response:
			3.7 mm speculum + anesthesia		Dear sir
					sorry i don't have the data that you asked
					in the article mentioned all the information of the study.
					sincerely
					R. Sagiv

Table 4 continued

References	Type	*N* total	Arms	N (VAS score 4–10)	How data were collected
Ekin et al. [10]	RCT		3.7 mm vaginoscopic 3.7 mm speculum + anesthesia		Email sent 13-08-2014 15:40 Response: Dear Dr.Paulo Daily we perform about 4-5 ofis hysteroscopy procedures. We have no previous data on visual analog scale of these patients. Dr.Murat Ekin
Unfried et al. [16]	RCT		3.7 mm rigid 3.6 mm flexible		Email sent 13-08-2014 17:51. No Response
Soriano et al. [25]	RCT		2.7 mm flexible 2.7 mm flexible + anesthetic		Email sent 08-02-2015 20:00. No Response
Floris et al. [26]	RCT		3.8 mm + placebo 3.8 mm + tramadol		Email sent 13-08-2014 16:08. No Response
De Carvalho Schettini et al. [29]	Prospective		4 mm 5 mm		Email sent 13-08-2014 17:12. No Response
Cicinelli et al. [16]	RCT		3.mm 5 mm		Email sent 13-08-2014 19:01. Response venerdì 29 agosto 2014 17.19 Dear Dr. Paulo, I apologize for delay in giving you a feedback. I was in vacation and I have just rear your request. I will try to collect data that you need and I will send you as soon as possible if you still need of them. Looking forward to hearing from you, I send you my best regards. Prof. Ettore Cicinelli—No further answer
De Placido et al. [17]	RCT		3.5 mm 5 mm		Email sent 13-08-2014 15:56. No Response
Pluchino et al. [18]	RCT		3.5 mm 5 mm		Email sent 13-08-2014 17:01. No Response

The arm of each study chosen for analysis are given in italics

from 0 to 10 and should be comparable. He mentions only unacceptable pain (VRS >7). VRS and VAS are both adequate and accurate for pain rating [58]. Rullo's [45] report specifically states that data he publishes refer to intolerable pain in mini-hysteroscopy. Finally, in Campo's [21] work, revision authors accepted failure rate as indicative of severe pain, for it is the most common cause for stopping the procedure.

Main findings

Mini-hysteroscopy remains painful for at least 13 % of women if cut-off for moderate pain is set at VAS ≥5 but it reaches over thirty percent if cut-off switches to a more acceptable and consensual value of VAS ≥4.

Angelis in 2003 wrote "The main purpose of our Gynecological Endoscopy Unit has always been to diminish the level of pelvic pain or discomfort felt by the patient during OH in order to make this procedure acceptable and well tolerated; our aim was to make it 'pain-free' and therefore widespread as against its presently limited application in Italy [7]." We believe this goal has not yet been accomplished.

Strengths and limitations

Both RCT and well-designed PT are very consistent and show that mini-hysteroscopy is not painless for a significant number of women.

Acknowledging the enormous benefit of this low-cost and very effective diagnostic gynecological workup tool

for the general population, authors cannot ignore some women may endure significant distress.

Limitations of this study include difficulty in obtaining accurate figures from original articles and the fact that most trials are still focused on proving it is feasible, rather than accepting the fact, and also the responsibility of health care providers to look further beyond this boundary: pain is still a problem in hysteroscopy. For full details on scrutinized studies, please see Table 4.

Interpretation (findings in light of other evidence)

Mini-hysteroscopy may not be as painless as previously thought and may even be very painful for nearly thirty percent of women. Investigation on ways and techniques to alleviate pain in hysteroscopy should continue. Cooper's and Ahmad's meta-analysis studies on effect of local anesthesia may prove valuable and show the way to do just that.

Although retrospective, Vinagre [59] describes a new endoscopic anesthetic technique using 35 cm long Cook® Williams Cystoscopic Injection Needle. Their results may provide a new insight into hysteroscopic anesthesia.

Conclusions

From evidence gathered, we must conclude that mini-hysteroscopy is painful for a non-negligible numbers of women and investigation on pain control should be continued.

Compliance with ethical standards

Conflict of interest The authors have no conflict of interest with any institution private or public.

Ethical standards No funding and no ethical approval was considered necessary.

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Paper number three: *"Hysteroscopy and pain: what risk factors should we consider in office hysteroscopy? Are there really any?"*

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Research Article

Hysteroscopy and pain: what risk factors should we consider in office hysteroscopy? are there really any?

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ABSTRACT

Background: Office hysteroscopy is the gold standard in abnormal uterine bleeding and an indispensable tool in modern gynecology. It is becoming increasingly popular leading to examinations and even operations without anesthesia as it is accurate, cheap and well tolerated. However, pain is still a limitation. The objective of the study was to determine if pain perception is linked to clinical predictors and how well they correlate with pain score.
Methods: Prospective observational trial enrolled one hundred and four women; four cases were excluded. One hundred cases were included and analyzed. Selection criteria: patients scheduled for Office Hysteroscopy who accepted to participate and had no contraindication for procedure.
Results: A ten centimeter visual analogue scale was used for pain evaluation. Presumed variables such as menopause, pelvic pain, previous cesarean section and cervical surgery, and body mass index were analyzed by ordered regression using standard statistical software tools.
Conclusions: Correlation between predictive factors and pain reporting showed no significance ($p>0.05$) except for body mass index which was found to significantly correlate to discomfort ($p<0.05$).

Keywords: Office hysteroscopy, Pain, Predictive factors

INTRODUCTION

In the past fifteen years gynecological care has shifted from hospital care to mostly outpatient interventions with added quality and reduced costs, making it affordable for generalized use. Hysteroscopy as a routine technique is recent, but it all started in 1967 when Fritz Menken used a pediatric cystoscope to examine the womb,[1] allowing direct visualization[2] and diagnosis.[3-6] It is now a day considered the gold standard in investigating uterine abnormal bleeding.[7-10]

Examinations and even operations are performed without anesthesia using Office Hysteroscopy (OH) and it is becoming increasingly popular; modern mini-hysteroscopes are slenderer (outer sheet between 3.1 and 3.6 mm) as opposed to "conventional" hysteroscopes (outer sheet of 5mm diameter) and therefor avoid cervical dilation. Slimmer scopes have been proven to associate to lower pain score at OH and there may be a cutoff around 3.5mm below which reduction in size does not further reduce pain.[11] Other improvements such as misoprostol administration prior to examination and the vaginoscopic no-touch approach seem to increase pain tolerance.[12-14]

De Angelis in 2003 wrote "The main purpose of our Gynecological Endoscopy Unit has always been to diminish the level of pelvic pain or discomfort felt by the

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patient during office hysteroscopy in order to make this procedure acceptable and well tolerated; our aim was to make it `pain-free' and therefore widespread as against its presently limited application in Italy."[15] But, despite the enormous success of hysteroscopy, the procedure is not yet painless.[16]

Cicinelli[17] in 2007 published a paper where cesarean section, menopause and chronic pelvic pain were found to significantly influence pain perception (group A patients who reported no pain on a zero to five pain reporting score had lower incidence of these factors and group B where patients reported mild to severe pain). Fonseca in 2014[18] while evaluating predictors of unacceptable pain, found significance only with pain (dysmenorrhea) and hysteroscopist experience. Sessa[19] did not find association between cesarean section and pain. Raymundo[20] found body mass index (BMI) and history of previous curettage to lower pain perception, while menopause and dysmenorrhea would predict higher pain score; association as a determinant however was low. Fonseca in 2009[21] evaluated uterine retroversion as pain predictor and concluded there was no association with pain at hysteroscopy. Finally Mazzon[22] found a protective role in parity, while cervical synechiae and duration of procedure correlated with higher visual analogue score (VAS) for pain.

OH patients may have higher VAS scores with longer waiting time[23,24] and distractions such as music may be associated with lower pain and anxiety.[25] But the question remains, are there clinical predictors associated with pain perception at hysteroscopy? Could theses predictors help select women who would benefit from analgesia or anesthesia?

METHODS

From March to June 2015 patients one hundred and eighteen patients scheduled for OH at Centro Hospitalar Tondela-Viseu, Portugal were invited to enroll in this prospective observational study. Of theses one hundred and four accepted to participate but four cases had incomplete data and were excluded. One hundred cases were included and analyzed. The study was approved by the Institutional Review Board and conducted in compliance with the protocol, the Declaration of Helsinki, the Good Epidemiological Practice, and all applicable laws and regulations.

Inclusion criteria

All women with scheduled OH were considered candidates. Only those who accepted to participate, had no acute infection, were not pregnant and had sufficient understanding of the aim of this study were included. They were fully informed that whether they chose or not to participate, procedure would be the same. All others were excluded (Figure 1).

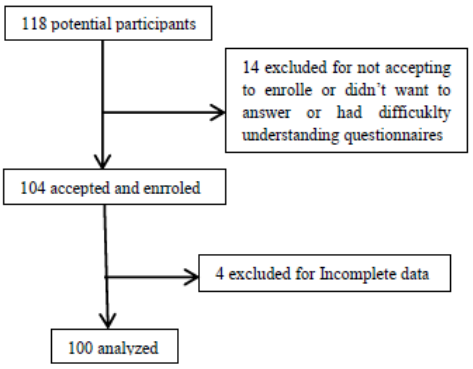

Figure 1: Flow diagram of selection of women.

Population characteristics are described on Table 1 and as shown, there's is a wide variation in age and body weight; fifty-five percent of women were menopausal.

Table 1: Population Characteristics.

	N=100	Minimum	Maximum	Mean	SE
Age		28	84	54.61	13.296
Gesta		0	9	2.19	1.376
Body weight		46	103	68.27	12.203
Height		145	179	159.13	6.447
C-section	21	0	3	.33	.697
Nuligest	9				
Parous	91				
Menopause*	55				
Fertile	45				

*last menses more than twelve months and woman not on hormone therapy

Women were referred to hysteroscopy to study common gynecological conditions: menorrhagia, post-menopausal bleeding, sonographic thickened endometrium and sterility (Table 2).

Table 2: Reason for hysteroscopy.

Frequency	
Menorrhagia	19
Post-menopausal bleeding	15
Thick endometrium	63
Sterility	3
Total	100

Hysteroscopy was performed using the vaginal no touch approach with a 3.5mm outer sheet device (2.9mm optics either from Fiegert Endotech® Tuttlingen, Germany or Karl Storz Hopkins® Tuttlingen, Germany) with a fore oblique 30° mini-hysteroscopy. An Ackermann® xenon

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light source and a constant flow Richard Wolf ® hystero pump, using saline at eighty mm of mercury was standard in procedure. A 3CCD endocam® enable vision on a screen. Misoprostol had been prescribed to be applied intra-vaginal the previous night.

At the end of procedure a nurse would show the woman a ruler having on the side facing the patient a straight 10cm line with markings "no pain" at left end and "maximal pain" on the right. A sliding courser was freely placed by the patient over the line where she reported her pain experience. At the back the ruler was graded in millimeters allowing healthcare personnel (nurse) to read results of patient scoring. Authors chose to value centimeters and only whole numbers were taken into account (e.g. 0 to 9 mm score zero, 1 to 1.9 mm scored one and so forth).

Statistical analysis was performed with SPSS 22.0 IBM for windows and in a statistical hypothesis test with a p value <0.05 the effect was considered significant so confidence intervals are reported with 95% confidence level. We conducted multivariate ordered logistic regression analysis. We explored the effect of menopause, dysmenorrhea and history of menorrhagia, parity of women, previous cervical surgery and age in pain score. We tested the proportional odds assumption using a score test.

RESULTS

Hysteroscopy was complete in ninety three cases and failed in seven. Those failures were rescheduled for the same procedure two weeks later. Four cases were not successful at this second attempt and were then scheduled to hysteroscopy under anesthesia. All cases were analyzed irrespective of completion of procedure.

Hysteroscopy findings are as shown in table 3 and include normal cavity, polyp, endometrial hyperplasia, carcinoma, uterine septum and submucosal and intramural mioma.

Table 3: Hysteroscopy diagnosis.

		Frequency
Valid	normal cavity	35
	polyp	45
	hyperplasia	1
	carcinoma	4
	septum	1
	mioma	7
	incomplete visualization	7
	Total	100

Taking into account pain scoring is ordinal; we performed an ordered logistic regression which did not find significance in pain reporting with menopause, dysmenorrhea, and history of menorrhagia, parity of women, previous cervical surgery or age. We did, however, find significance (p<0.05) in Body Mass Index (BMI) as seen on Table 4, although the effect size was small. We also tested the fitting of the model by performing a parallel lines test which showed a p value = 1.000. The goodness of the fit of the model can be evaluated taking into account the pseudo R squares (Table 5).

Table 4: Ordinal logistic regression.

Source	exp(B)	Wald Chi-Square	Sig.
Menopause	0.957	0.005	0.941
Dysmenorrhea	0.892	0.052	0.820
Menorrhagia	0.546	1.770	0.183
Parous	0.726	0.088	0.766
BMI	0.849	4.996	0.025
Cervical surgery	0.780	0.094	0.760
Age	1.023	1.054	0.305

Score test of the proportional odds assumption p=1.000

Table 5: Pseudo R-Square.

Pseudo R-Square	
Cox and Snell	.131
Nagelkerke	.132
McFadden	.031

Link function: Logit

E.g.: The Nagelkerke R Square indicates the model can account for 13.2% of the variance in tier of entry.

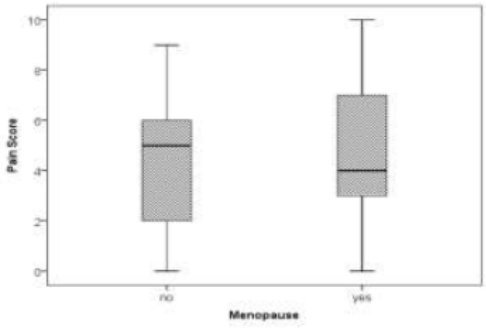

Figure 2: Boxplot pain score verses menopause.

Box plots comparing women before and after menopause, with or without history of dysmenorrhea and with and without cervical surgery, surprisingly showed a trend to lower pain reporting when each of these variables was "yes" (Figures 2, 3 and 4). We would expect menopause, painful menstruation and history of cervical surgery to associate with higher scores which doesn't seem to be the case. Regression results however had no statistical significance as shown on table 4.

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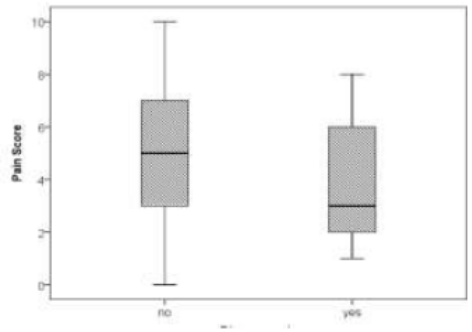

Figure 3: Boxplot pain score verses dysmenorrhea.

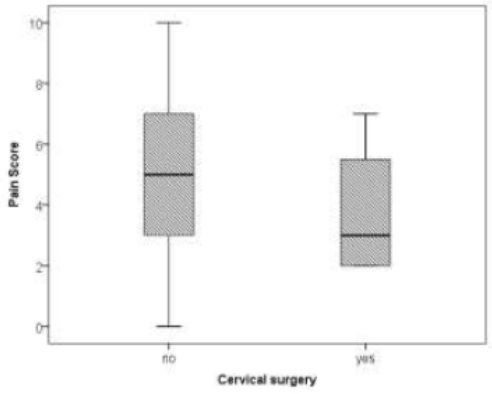

Figure 4: Cervical surgery.

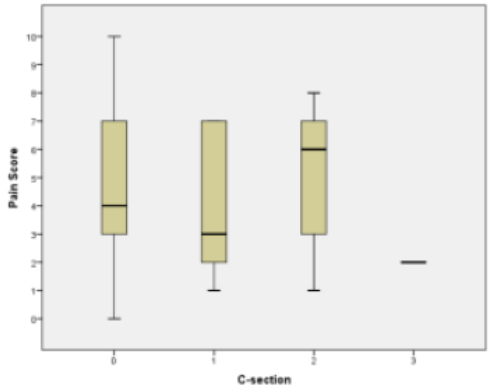

Figure 5: Pain reporting and Cesarean-section.

Finally, cesarean section (C-section) was not included in our regression to avoid collinearity with parity. Boxplots comparing women without C-section and with one, two or three occurrences showed mix results but no clear increase in pain at hysteroscopy (Figure 5).

DISCUSSION

It is interesting to find BMI is associated with lower perceived pain at hysteroscopy and this finding goes in line with Raymundo's results.[20]

Increased levels of estradiol, a significant reduction of sex hormone binding-globulin (SHBG) and a rise in circulating androgens, all being mediated by obesity-related changes in insulin and having a direct relationship to augmented BMI have been well recognized.[26-28] Obesity also gives rise to an increased total body aromatization (in adipose tissue) and consequently moderately elevated estrogen serum levels in overweight postmenopausal women are, in theory, to be expected.

Insulin and SHBG have a 'gonadotropic' effect and insulin and Insulin-like growth factor one (IGF-I) activity may be of less significance before menopause than after its occurrence. In a fertile woman circulating sex-steroid hormones are under the tight control of hypothalamic and pituitary hormones: Luteinizing Hormone (LH) and Follicle-Stimulating Hormone (FSH) and regulated by powerful feed-back mechanisms, which subsequently subside after menopause.

Decreased SHBG concentrations, characteristic of obesity, would lead to an increase in free testosterone.[26] Therefor there is an inverse correlation between SHBG with the calculated free levels of both testosterone and estrogens. Studies have suggested that the adipose tissue, with its 17b-hydoxysteroid dehydrogenase activity, may also be an important site of peripheral testosterone production and conversion to estrogens (namely estradiol or estrone).[26,29]

Gynecologists are well aware of obesity, diabetes and hypertension as risk factors for endometrial (and other female hormone dependent) cancers and poor response to aromatase inhibitor treatment in hormone dependent malignancies.[28]

Target tissues (vaginal, cervical and endometrial cell lining) response to these elevated hormones would expectedly counteract atrophy, contributing to eutrophic (hormone dependent) mucosal development and thus might help explain greater ease of the procedure and the lower pain perception in obese women.

CONCLUSIONS

From our results we conclude menopausal state, previous history of cervical surgery, dysmenorrhea, or abnormal uterine bleeding might not have a significant effect on pain.

On the other hand obesity is a reliable predictor of lower pain perception. It is most likely the single most important natural factor which might reduce pain in OH.

Strength's and limitations

This observational study gives us robust information regarding pain and menopausal state compared with pre-menopausal as 55% of women were menopausal upon examination. Elevated BMI has shown to be significant in reducing pain and theoretically this makes sense as, we know, there is a higher level of circulating hormones in these women.

Another putative factor which is parity, seems well represented in this series. It did not show to be associated with significant influence in pain scores. History of previous cervical surgery has few cases and might be less well represented so authors admit larger studies including more cases of women subjected to prior surgery, could help to better understand what role this factor might have in nociceptive experience following hysteroscopy.

ACKNOWLEDGEMENTS

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Review Board and conducted in compliance with the protocol, the Declaration of Helsinki, the Good Epidemiological Practice, and all applicable laws and regulations

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Paper number four: *"Pain, anxiety and patient satisfaction in office hysteroscopy, is there a link? Are patient satisfaction questionnaires reliable?"*

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Research Article

Pain, anxiety and patient satisfaction in office hysteroscopy, is there a link? Are patient satisfaction questionnaires reliable?

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ABSTRACT

Background: Office hysteroscopy is becoming increasingly popular leading to examinations and operations without anesthesia. Anxiety is always present before an aversive medical intervention and may play a role in pain perception. The objectives of the study were to determine if pain perception is linked to anxiety and how well patient satisfaction questionnaires correlate with pain.
Methods: Prospective observational study enrolled one hundred and four women. One hundred cases were included and analyzed. Patients scheduled for office hysteroscopy, who accepted to participate and were able to answer questionnaires.
Results: A ten centimeter visual analogue scale was used for pain evaluation and the State anxiety-trait inventory for adults questionnaires for anxiety assessment. Three other satisfaction questionnaires, each consisting of three answers, were also administered and investigated. Analysis was performed using SPSS 22.0 IBM for windows software tools.
Conclusions: Correlation between anxiety and pain reporting showed no influence with anxiety trait (p value = 0.4170) and a mild correlation with anxiety state (p value = 0.146). Classification of pain into "no pain", "mild pain", "moderate pain" and "severe pain", should be revised in office hysteroscopy: for visual analogue scale, scores of 2.5 to 3 cm correspond to the lower boundary of moderate pain and scores above limit 6.5 cm should define pain as severe. Satisfaction questionnaires significantly correlated to discomfort (p value <0.001) and may be a practical option to assess tolerance of medical procedures with excellent sensibility and specificity.

Keywords: Office hysteroscopy, Anxiety, Pain, Satisfaction questionnaires

INTRODUCTION

In 1967 Fritz Menken used a pediatric cystoscope to examine the womb.[1] Hysteroscopy is nowadays a routine technique, allowing direct visualization and diagnosis and is considered gold standard in uterine abnormal bleeding.[2-10]

Office hysteroscopy (OH) is becoming increasingly popular, leading to examinations and even operations without anesthesia, as modern mini-hysteroscopes avoid cervical dilation, misoprostol administration facilitates operations and the vaginoscopic "no-touch" approach improves tolerance.[11-13]

Anxiety is almost always present before an aversive medical intervention and may play a role in pain perception.[14-18] There seems to be a positive association between anxiety level and visual analog scale (VAS) pain reporting, and in some cases nervousness may lead to catastrophizing (exaggerated negative orientation toward pain stimuli).[17,18] Pain can be predicted with a measure of catastrophizing one week prior to scheduled appointment for procedure.[19]

The State anxiety-trait inventory for adults (STAI) Form Y1 (administered for anxiety trait) and Form Y2 (administered for anxiety state) have been validated for evaluation and scoring of anxiety.[20,21] Both consist of a self-administered twenty question sheet with four possible answers (not at all, somewhat, moderately so and very much so). Score values range from twenty to a maximum of eighty in each subscale. In general the higher the score, the more anxious the patient is and it has been suggested that scores of thirty-nine to forty in young adults, and fifty-four to fifty-five in older adults are indicative of clinically significant anxiety.[21,22] There are Portuguese versions of these questionnaires which have been validated.[23]

OH patients may have higher VAS scores with longer waiting time and women with higher STAI scores may experience more pain or indeed there may not be any correlation between STAI and VAS scores.[24-26] Distractions such as music may be associated with lower pain and anxiety.[27]

As to patient satisfaction questionnaires, how well do they correlate with pain score? De Iaco wrote "one-third of women experienced severe pain, although most (83%) claimed they were willing to have a repeat procedure under the same conditions".[28]

There are two questions we will try to answer: Is pain perception linked to anxiety? And how well do patient satisfaction questionnaires correlate with pain score?

METHODS

From March to June 2015, one hundred and eighteen patients scheduled for OH at centro hospitalar tondela-viseu, Portugal were invited to enroll in this prospective observational study. Of theses one hundred and four accepted to participate but four cases had incomplete data and were excluded. One hundred cases were included and analyzed. The study was conducted in compliance with the protocol, the declaration of Helsinki, the good epidemiological practice, and all applicable laws and regulations. This work was supported by Portuguese iBiMED - Institute for Biomedicine and the Portuguese Foundation for Science and Technology (FCT-Fundacao para a Ciencia e a Tecnologia) within projects: UID/BIM/04501/2013

Inclusion criteria

All women with scheduled OH were considered candidates. Only those who accepted to participate, had no acute infection, were not pregnant and had sufficient understanding of Portuguese reading and writing to be able to answer questionnaires were included. They were fully informed that whether they chose or not to participate, procedure would be the same. All others were excluded (Figure 1).

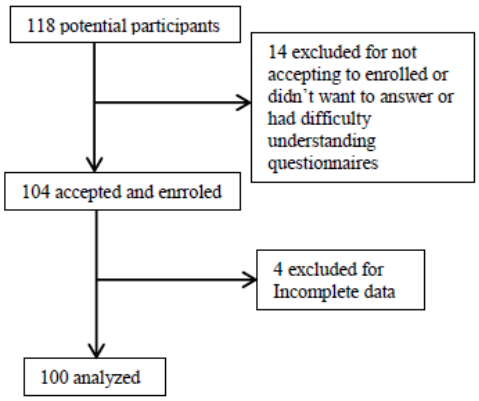

Figure 1: Flow diagram of selection of women.

Before examination, a STAI Y1 and a STAI Y2 (www.mindgarden.com) questionnaire was offered to participants, with a thorough explanation of how to answer, stressing replies were confidential, couldn't be traced to patient by unauthorized personnel and should be as honest as possible. Population characteristics are described on Table 1.

Table 1: Population characteristics.

	N= 100	Mini-mum	Maxi-mum	Mean	SE
Age		28	84	54.61	13.296
Gesta		0	9	2.19	1.376
Body weight		46	103	68.27	12.203
Height		145	179	159.13	6.447
C-section	21	0	3	0.33	0.697
Nuligest	9				
Parous	91				
Menopause*	55				
Fertile	45				

*Last menses more than twelve months and woman not on hormone therapy

Table 2: Reason for hysteroscopy.

		Frequency
Valid	Menorrhagia	19
	Post-menopausal bleeding	15
	Thick endometrium	63
	Sterility	3
	Total	100

Women were referred to hysteroscopy to study common gynecological conditions: menorrhagia, post-menopausal bleeding, sonographic thick endometrium and sterility (Table 2).

Hysteroscopy was performed using the vaginal no touch approach with a 3.5mm outer sheet device (2.9 mm optics either from Fiegert Endotech® Tuttlingen, Germany or Karl Storz Hopkins® Tuttlingen, Germany) with a fore oblique 30° mini-hysteroscopy. An Ackermann® xenon light source and a constant flow Richard Wolf ® hystero pump, using saline at eighty mm of mercury was standard in procedure. A 3CCD endocam® enable vision on a screen. Misoprostol had been prescribed to be applied intra-vaginal the previous night.

At the end of procedure a nurse would show the woman a ruler having on the side facing the patient a straight 10 cm line with markings "no pain" (left end) and "maximal pain" (on the right end). A sliding courser was freely placed by the patient over the line matching to her pain experience. At the back the ruler was graded in millimeters allowing healthcare personnel (nurse) to read results of patient scoring. Authors chose to value centimeters and only whole numbers were taken into account (e.g. 0 to 9 mm score zero, 1 to 1.9 mm scored one and so forth). Total duration of procedure did not exceed five minutes.

After scoring patient's VAS, each women was asked to answer three satisfaction questions: Procedure was easy? (With three possibilities "easy", "some discomfort" or "hard to endure"); second question pain medication (with three possibilities "very important to have medication", "important to have medication" or "not important to have medication") and a third question would you take medication next time? (With three possibilities "no", "don't know" or "would take").

Statistical analysis was performed with SPSS 22.0 IBM for windows and in a statistical hypothesis test with a p value <0.05 the effect was considered significant. The confidence intervals are consequently reported with a 95% assurance level. The normal goodness of fit testing was applied for all quantitative variables. Kolmogorov-Smirnov test revealed that for almost all quantitative variables the normal distribution fit is rejected. In accordance we performed non parametric statistical tests. For details please refer to annex table at the end of this article. Kruskal Wallis test was used to evaluate the association between the pain score and the satisfaction variables, Spearman's correlation was used to correlate anxiety and pain, and finally receiver operating characteristic (ROC curve) were constructed with answers from satisfaction questionnaires in order to establish cutoff points.

RESULTS

Hysteroscopy was complete in ninety three cases and failed in seven. Those failures were rescheduled for the same procedure a few weeks later. Four cases were not successful at this second attempt and were then scheduled to hysteroscopy under anesthesia. All cases were analysed irrespective of completion of procedure and pain score results refer to the first attempt at hysteroscopy.

Hysteroscopy findings are as shown in Table 3 and include normal cavity, polyp, endometrial hyperplasia, carcinoma, uterine septum and submucosal and intramural mioma.

Table 3: Hysteroscopic diagnosis.

		Frequency
Valid	Normal cavity	35
	Polyp	45
	Hyperplasia	1
	Carcinoma	4
	Septum	1
	Mioma	7
	Incomplete visualization	7
	Total	100

Mean pain and STAI scores are shown on Table 4, showing percentiles and maximum and minimum values.

Table 4: Pain and anxiety scores.

		Mean pain score	STAI-Y1	STAI-Y2
N	Valid	100	100	99
Minimum	0	21	20	Minimum
Maximum	10	69	73	Maximum
Percentiles	25	2.25	36.00	36.00
	50	4.50	45.50	43.00
	75	7.00	52.00	49.00

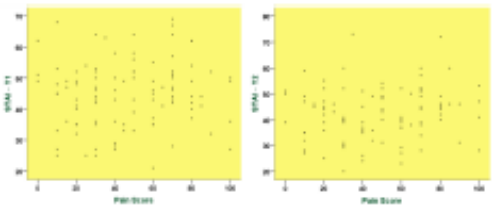

Figure 2: Scatter plot pain score versus anxiety score.

The association between variables was evaluate by Spearman's correlation. There seems to be a weak correlation between anxiety and pain score which is not significant (p value>0.05): 8% correlation between pain score and STAI Y1 and 15% for STAI Y2 (Table 5). Scatter plots visually express this lack of correlation and so probably anxiety is not a significant factor in pain perception (Figure 2).

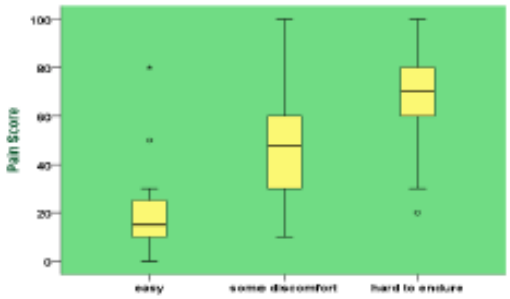

Figure 3: Procedure was easy?

Table 5: Procedure was easy?

Test statistics[a,b]			
	Pain Score	STAI - Y1	STAI - Y2
Chi-Square	45.625	2.568	7.513
Asymp. Sig.	0.000	0.277	0.023
a. Kruskal Wallis test			
b. Grouping variable: Procedure was easy			

The Kruskal Wallis test was used to evaluate the association between the pain score and the satisfaction variables (three questions shown in Figures 3, 4 and 5 coupled with STAI scores results). Once again, anxiety scores do not show significant results (p value>0.05) except for question number one and for the Y2 questionnaire (state anxiety) which showed a modest association between anxiety and pain (p value = 0,023) as shown in Figure 3.

In contrast, this same Kruskal Wallis test shows significant association between pain score and replies from satisfaction questionnaires (p<001). The boxplot below each statistical test show patients answers to be significant and consistent. The higher the pain score, the more likely women will complain and will be willing to accept medication for pain relief (Figures 5, 6 and 7).

Table 6: Pain and medication.

Test statistics[a,b]			
	Pain Score	STAI - Y1	STAI - Y2
Chi-Square	27.416	1.038	2.933
Asymp. Sig.	0.000	0.595	0.231
a. Kruskal Wallis test			
b. Grouping variable: Pain medication			

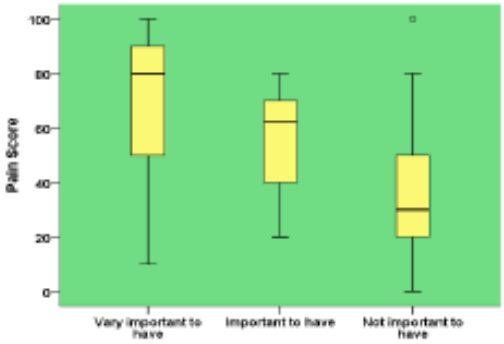

Figure 4: Pain and medication.

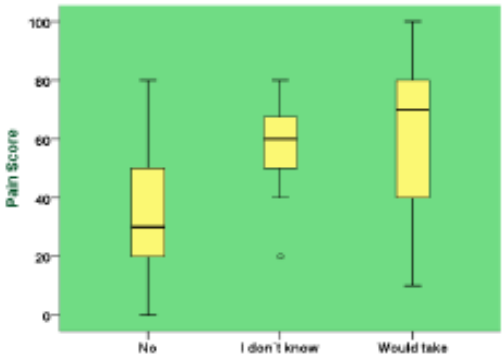

Figure 5: Would you take medication next time?

Table 7: Would you take medication next time?

Test statistics[a,b]			
	Pain Score	STAI - Y1	STAI - Y2
Chi-Square	18.353	0.915	0.086
Asymp. Sig.	0.000	0.633	0.958
a. Kruskal Wallis test			
b. Grouping variable: Would you take medication next time?			

We further explored the satisfaction questionnaires trying to understand how well they fitted to pain score and if some estimate regarding pain perception could be made from these simple answers. Replies were broken down to binary responses for analysis. First we considered "easy versus not easy" (this latter group aggregating some discomfort and hard to endure responses) giving a total of twenty two for "easy" versus seventy eight for "not easy". A second set of binary responses was considered involving "tolerable" (joining up easy and some discomfort groups) versus "hard to endure" giving a total of twenty nine for "tolerable" and seventy one for "hard to endure".

Table 8: ROC curve for pain score: easy (not painful) procedures.

Area under the curve				
Test result variable(s): Pain score				
Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% confidence interval	
			Lower bound	Upper bound
0.905	0.044	0.000	0.819	0.990
The test result variable(s): Pain score has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.				
a. Under the nonparametric assumption				
b. Null hypothesis: true area = 0.5				

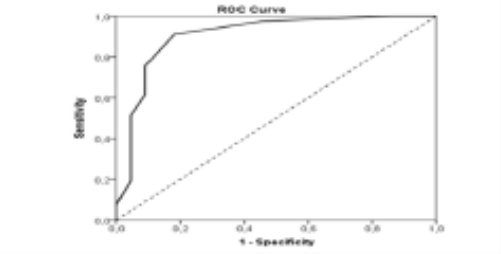

Figure 6: ROC curve for pain score: easy (not painful) procedures.

These responses allowed a ROC curve to be constructed from theses binary responses to identify procedures as easy and hard to endure (Figures 6 and 7). From the ROC curve we calculated a Yoden index (=sensitivity+specificity-1) and for each plot a cutoff point was attained. In Table 11 see the cutoffs matching to the maximum Yoden index values highlighted in yellow. Testing of the area under a ROC curve was conducted and the statistical results were significant (p value <0.001).

Table 9: ROC curve for pain score for hard to endure (painful) procedures.

Area under the curve				
Test result variable(s): Pain score				
Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% confidence interval	
			Lower bound	Upper bound
0.831	0.045	0.000	0.742	0.920
The test result variable(s): Pain score has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.				
a. Under the nonparametric assumption				
b. Null hypothesis: true area = 0.5				

Table 10: Yoden index constructed from ROC curve.

Coordinates of the Curve (from curve in Figure 6)				Coordinates of the Curve (from curve in Figure 7)			
Test Result Variable (s):	Pain Score			Test Result Variable (s):	Pain Score		
Positive if greater than or equal to[a]	Sensitivity	1 - Specificity	Yoden index	Positive if Greater Than or Equal To[a]	Sensitivity	1 - Specificity	Yoden index
-1.00	1.000	1.000	0.000	-1.00	1.000	1.000	0.000
0.50	1.000	0.864	0.136	0.50	1.000	0.958	0.042
1.50	0.974	0.455	0.520	1.50	1.000	0.803	0.197
2.50	0.910	0.182	**0.728**	2.50	0.966	0.662	0.304
3.50	0.756	0.091	0.666	3.50	0.862	0.507	0.355
4.50	0.615	0.091	0.524	4.50	0.828	0.366	0.461
5.50	0.513	0.045	0.467	5.50	0.793	0.254	0.540
6.50	0.372	0.045	0.326	**6.50**	0.690	0.141	**0.549**
7.50	0.192	0.045	0.147	7.50	0.414	0.056	0.357
8.50	0.077	0.000	0.077	8.50	0.172	0.014	0.158
9.50	0.051	0.000	0.051	9.50	0.103	0.014	0.089
11.00	0.000	0.000	0.000	11.00	0.000	0.000	0.000
The test result variable(s): Pain Score has at least one tie between the positive actual state group and the negative actual state group.							
a. The smallest cutoff value is the minimum observed test value minus 1, and the largest cutoff value is the maximum observed test value plus 1. All the other cutoff values are the averages of two consecutive ordered observed test values.							

Test variable is "pain score" and State variable is question "procedure was easy" dichotomized as: easy vs not easy

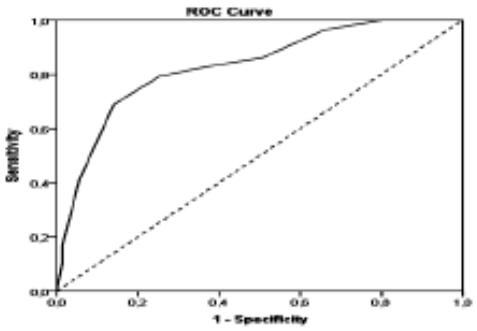

Figure 7: ROC curve for pain score for hard to endure (painful) procedures.

Table 11: Two by two cross-tabulation for procedure difficulty vs pain.

Easy versus not easy (discomfort + hard to endure)				
VAS	Procedure was		Total	
	Easy		Not easy	
Pain	(0,2)	18	7	25
	(3,10)	4	71	75
Total	22		78	100

The best cutoff points matched VAS 2.5 and VAS 6.5 for answer shifts, and we split results into categories "easy" (zero to two) "some discomfort" (three to six) and "hard to endure" (seven to ten).

We then used a two by two cross-tabulation for the first question "procedure was easy" (with three possible answers: "easy", "some discomfort" or "hard to endure"). Replies analysed were easy versus not easy (which included "some discomfort" and "hard to endure"). We were able to then calculate sensitivity (94%) and specificity (72%) in predicting that hysteroscopy (when answers were "not easy" to tolerate) would correspond to VAS score above two (Table 11).

DISCUSSION

Angioli used music and found a positive distracting effect lowering pain in OH surgery and STAI Y1 post-operative scores compared with operation without music.[27] Carta on the other hand found waiting time (along with age and menopause) to be associated with increased pain but no increase in anxiety was found.[25] Gupta stated women in hysteroscopy outpatient units experience higher levels of anxiety than other patients in gynecology care.[26] Kokanali also found a positive correlation between waiting time and anxiety with increased pain scores.[24]

Our data do not support a correlation between STAI form Y1 (trait anxiety) and an increased pain score. As to STAY form Y2 (state anxiety), data showed a very modest correlation between state anxiety and pain.

We did however, find a significant correlation between satisfaction questionnaires and women's discomfort ($p<001$) and all three questions are consistent in responses.

Interpretation (findings in light of other evidence)

To the best of our knowledge this is the first study comparing satisfaction questionnaire answers to pain scoring and finding statistical significance in this comparison.

We find it quite significant that women tend to consider "easy" or acceptable, maneuvers with VAS scores up to approximately three centimeters. This cutoff has been considered the upper limit score for "mild" pain.[29-33] Not all authors agree: Jensen and Burckhardt suggest a higher cutoff of 4.4 centimeters. Our data suggest this threshold proposed by Jensen to be somewhat high and a VAS around three seems more acceptable and adequate for clinical evaluation of pain perception in OH.[34,35]

Use of simple questionnaires is reproductive and reliable and may help grade nociceptive experience into acceptable or unacceptable.

CONCLUSION

In our study, we did not find an association between anxiety and pain scores in women undergoing OH. Nevertheless our first satisfaction variable had significance with STAI-Y2 ($p = 0.023$), although effect was weak (Figure 3). This may imply state anxiety may very slightly influence pain.

Our data also recommends classification of pain into "no pain", "mild pain", "moderate pain" and "severe pain", should be revised in OH. Contrary to Jensen and Burckhardt our figures supports that for VAS evaluation, scores of 2.5 to 3 cm correspond the lower boundary of moderate pain and scores above the upper limit of VAS 6.5 cm should define pain as severe.

Questionnaires on patient satisfaction may be useful and are reliable. They reflect closely patient nociceptive experience. Evaluation of acceptance of an unpleasant medical intervention with a three answer questionnaire accurately reflects nociceptive experience compared to VAS evaluation. These three answer questions are simple and more practical to use than VAS scoring. Three answer questionnaire objectively asking women about tolerability may be accurate, easy to use and give healthcare providers an alternative useful tool for assessing patient discomfort, when performing aversive medical interventions. Sensibility and specificity are both excellent for theses inquiries.

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Paulo AA et al. Int J Reprod Contracept Obstet Gynecol. 2016 Mar;5(3):642-650

Annex table.

	Kolmogorov-Smirnov*		
	Statistic	df	Sig.
Age	0.066	100	0.200*
Age at menopause	0.137	55	0.012
Gesta	0.235	100	0.000
Vaginal deliveries	0.187	100	0.000
C-section	0.472	100	0.000
Body weight	0.106	100	0.008
Height	0.096	100	0.023
Diastolic blood pressure (before) mm HG	0.071	100	0.200*
Systolic blood pressure (before) mm HG	0.050	100	0.200*
Diastolic blood pressure (after) mm HG	0.090	100	0.043
Systolic blood pressure (after) mm HG	0.071	100	0.200*
Oximetry before (% O2)	0.486	100	0.000
Oximetry after (% O2)	0.486	100	0.000
pulse (before) (BMP)	0.084	100	0.078
pulse (after) (BMP)	0.097	100	0.020
Body mass index	0.120	100	0.001

* This is a lower bound of the true significance.

Paper number five: *"Office Hysteroscopy and pain control, a multicenter study comparing pain by scope size. Introducing the novel "hysteroscopic anaesthesia" technique"*

Clinical Obstetrics, Gynecology and Reproductive Medicine

Research Article

Office hysteroscopy and pain control, a multicenter comparison by scope size and introducing a novel "hysteroscopic anesthesia" technique

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Abstract

Background: Office hysteroscopy is an affordable and popular approach in gynecology, offering high quality and inexpensive care. It has been made possible by miniaturization of instruments along with a range of technical variations and innovations which have made the procedure tolerable in outpatient care units. Pain is still a problem and has not to date been adequately managed.

Objectives: Our main objective is to compare two centers where hysteroscopy is performed without general anesthesia or sedation in an office setting. In Lisbon a novel local anesthetic technique has been introduced when patients complained of pain. These centres have slightly different protocols namely in assessing pain and evaluating score results.

Materials and methods: This was a prospective observation multicenter study, comparing pain in office hysteroscopy with three groups: mini-hysteroscopy (3 mm scope), conventional (5 mm) hysteroscopy without anesthesia and (5 mm) hysteroscopy with "hysteroscopic anesthesia".

Data collection and analysis: We analyzed data from two centers involving one hundred and eighty one participants who completed the intervention. Pain was evaluated using a 10 cm visual analogue scale and a numeric rating scale. Analysis included the Kruskal-Wallis and Mann-Whitney Tests for the three groups and the Wilcoxon Signed Ranks Test for comparing repeated measurements. Results were discussed at 5% significance level.

Main results: Analysis revealed a significant reduction pain score (p value <0.001) in the group where "hysteroscopic anesthesia" was used.

Conclusions: Pain scores in office hysteroscopy can be lowered with "hysteroscopic anesthesia".

Introduction

Hysteroscopy allows direct visualization of unsuspected pathology, histological sampling, cancer staging and surgery. Office hysteroscopy (OH) is a high quality approach in gynecology.

Reduction in pain has led to performing examination and operations without anesthesia [1,2] and is associated to very low cost of gynecological care and justifies its generalized use [3]. Pain perception may vary among population subgroups [4,5].

The vaginoscopic no-touch approach [3,6-9] improved tolerance as data in a 2010 systematic review by Cooper *et al.* [9] demonstrated. Use of mini-hysteroscopes avoid cervical dilation and previous ripening with misoprostol facilitates operations [1,10]. Both rigid and flexible mini-histeroscopes reduce pain and may be adequate for examination [11] but rigid scopes seem to have superior optical properties [12].

CO_2 and normal saline are adequate for diagnostic outpatient hysteroscopy [13] as Cooper's 2010 systematic review on effect on pain concluded, but saline is more convenient if surgery is to be done [14].

Various interventions [15,16], medications [17,18], para-cervical block cocktails and conscious sedation have been suggested to control pain with mixed results [10,19-23]. Two systematic review in 2010, one by Ahmad *et al.* [24] and another by Cooper *et al.* [21] have however suggested a reduction of pain with local anesthetic, but "clinical significance of results is limited as the reduction in mean pain score is small" [24].

Vinagre *et al.* [25] describes a new endoscopic local anesthetic technique using 35 cm long Cook®Williams Cystoscopy Injection Needle ("hysteroscopic anesthesia").

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Key words: *hysteroscopy, pain, hysteroscopic anesthesia*

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Objectives

Our main objectives are: to determine if difference in scope diameters and if the use of a novel technic of local anesthesia shows statistical difference in pain scores during office hysteroscopy.

Materials and methods

From February to September 2015 one hundred and eighteen patients scheduled for OH at Centro Hospitalar Tondela-Viseu, Portugal and eighty one from Hospital das Forças Armadas – Polo de Lisboa, Portugal were enrolled in this prospective observational study. Of theses one hundred and four from Viseu and eighty one from Lisbon accepted to participate. Four cases from Viseu had incomplete data and were excluded. A total of one hundred and eighty one cases were included and analyzed (Figure 1). The study was approved by the Institutional Review Boards and conducted in compliance with the protocol, the Declaration of Helsinki, the Good Epidemiological Practice, and all applicable laws and regulations.

Hysteroscopy was performed using the vaginal no touch approach with a 3.5 mm outer sheet device (2.9 mm optics either from Fiegert Endotech® Tuttlingen, Germany or Karl Storz Hopkins® Tuttlingen, Germany) with a fore oblique 30° mini-hysteroscopy at Centro Hospitalar Tondela-Viseu and a 5 mm outer sheet device at Hospital das Forças Armadas Lisbon. An Ackermann® xenon light source with a constant flow Richard Wolf® hystero pump was used in Viseu and Endoflow® by Socomed in Lisbon; saline at eighty to one hundred mm of mercury was standard in procedures.

Protocol was slightly different in each institution: no anesthesia was provided in Viseu and in Lisbon, when women complained, a new endoscopic local anesthetic technique by means of 35 cm Cystoscopy Injection Needle named by Vinagre *et al.* [25] "hysteroscopic anesthesia" was used.

This technique is a modification of Skensved's "Hysteroscopically Guided Intramyometrial Local Anesthesia – The Focal Local" [26].

While performing vaginoscopy the surgeon assessed patient's tolerance. If pain made the procedure uncomfortable, 1% lidocaine was injected directly through the endoscope in the endo-cervical region at the site where the women felt pain with the cystoscopic needle in small amounts (commonly near the internal os). Further along the hysteroscopy, if discomfort arose from distension of the uterus, the operator would retrieve the instrument into the vagina and the uterosacral ligaments were also injected with lidocaine. In case of see-and-treat septoplasty, polypectomy or myomectomy anesthetic was injected at the base of the mass to be excised, allowing for pain control during operation. Total amount of anesthetic used was about five centiliters and did not in any case exceed 10 cc for safety reasons.

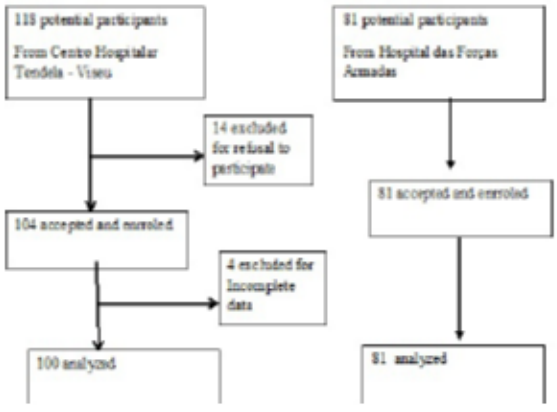

Figure 1. Flow diagram of selection of women.

Table 1. Patient characteristics.

	3.5 mm	(range)	5 mm	(range)	5 mm & anesthesia	(range)
n	100		52		29	
Menopause	45		19		6	
Age	54	(28-84)	61	(20-85)	67	(30-81)
BMI	26,2	(19.1-39.5)	26,6	(19.1-39.9)	27,6	(21.6-46.1)
Weight	65.50	(46-103)	68.00	(43-102)	66,00	(50-118)

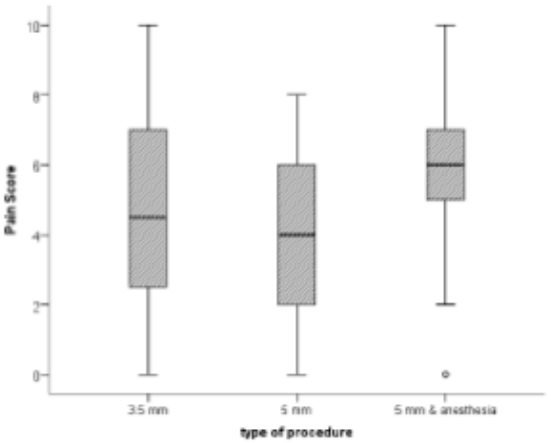

Figure 2. Pain score and type of procedure.

Pain scoring was evaluated using a 10 cm Visual Analogue Scale (VAS) in Viseu and a ten points Numeric Rating Scale (NRS) in Lisbon.

Three groups were so compared: 3.5 mm mini-hysteroscopy, 5 mm hysteroscopy without anesthesia and 5 mm hysteroscopy with anesthesia. Patient's mean age tends to be higher in Lisbon's 5 mm series and even higher in the 5 mm group with anesthesia. Other variables don't seem significantly different between groups (Table 1).

Statistical analysis was performed with SPSS 22.0 IBM for windows and in a statistical hypothesis test with a p value <0.05 the effect was considered significant so results are reported with 95% confidence level.

Results

We performed a Kruskal-Wallis test with the three groups and results showed there was at least one group of the three analyzed where pain score was significantly different. A plot comparing pain score in the groups can been seen in Figure 2. There seems to be a trend for higher pain score with menopausal state (Figure 3). As to other variables women's body mass index and weight was similar between the three groups (Figure 4) but mean age is higher and statistically

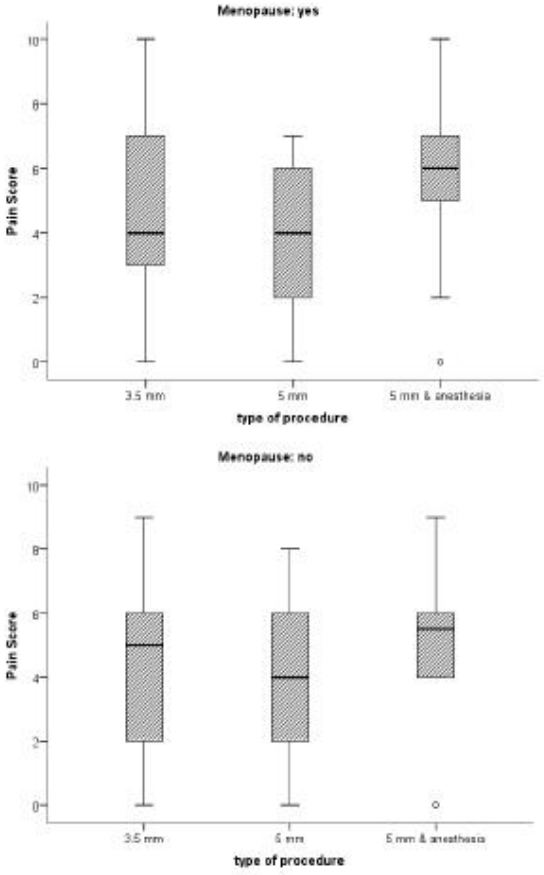

Figure 3. Menopause and pain.

significant in the anesthesia group (group of women who reported more pain and where lidocaine was administered).

Comparing groups two by two, the difference between pain score was demonstrated between 5 mm hysteroscopy and 5mm hysteroscopy with anesthesia groups. The Mann-Whitney test with Bonferroni correction (Table 2) showed significant differences between the three groups (p value=0.012). Comparing repeated measurements using the Wilcoxon Signed Ranks Test (5 mm group before anesthesia and 5 mm group after anesthesia) showed a significant reduction in pain as seen in Table 4 (p valeu <0.001).

Discussion

Our data found a trend for lower pain reporting with 3.5 mm versus 5 mm scopes (Table 3) as would be expected in line with a recent meta-analysis and review [27].

The study also suggests hysteroscopy with 5 mm scopes and "hysteroscopic anesthesia" is less painful than hysteroscopy without anesthesia in an office setting. As seen, mean pain scores before anesthesia including all 5 mm hysteroscopies are higher in the group which was subsequently treated with anesthesia (NRS around six) as compared to patients where no anesthesia was used (NRS around four) (Figure 5). The sub-group where anesthesia was used tends to be older (Figure 4) so, most likely the higher pain report is related to menopausal tissue atrophy. Significantly this group of women showed a dramatic decrease in discomfort after lidocaine (Figure 6).

Introducing "hysteroscopic anesthesia" to women in outpatient OH units offers relief from distress, having a statistically significant effect on pain score. This result seems even more noteworthy as both 5 mm hysteroscopy groups came from the same institution, was seen by the same personnel and protocol pain assessment used the same tool, namely NRS.

Table 2. Hysteroscopy and pain score.

3.5 mm vs 5 mm	p=0.168
3.5 mm vs 5 mm with anesthesia	p=0.291
5 mm vs 5 mm with anesthesia	p=0.012

* Mann-Whitney U test with Bonferroni correction

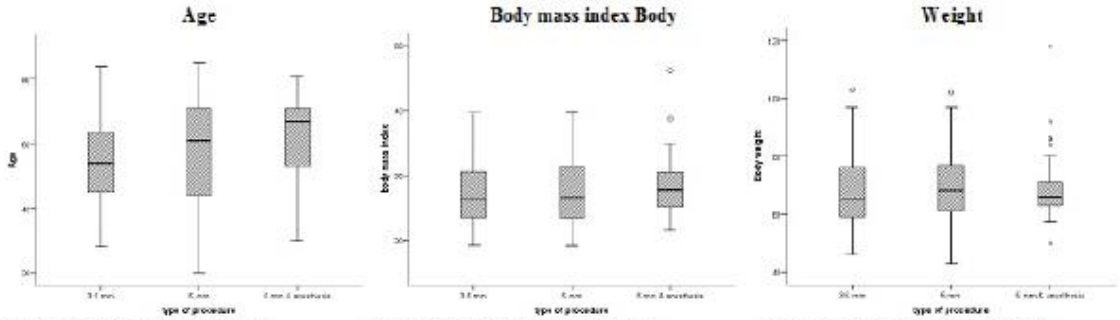

Figure 4. Comparison of age, body mass index and weight between the three groups.

N	Valid	100	81
	Missing	0	0
	Median	4.50	5.00
Percentiles	25	2.25	2.50
	50	4.50	5.00
	75	7.00	6.00

Pain Score Statistics[ab]

† a. type of procedure = 3.5 mm ‡ b.= 5 mm

Table 3. Mean pain score and quartiles for 3.5 mm and 5 mm hysteroscopy.

Table 4. Before and after hysteroscopic anesthesia.

Test Statistics[a]	Pain score post anesthesia - Pain Score
Z	-3.178[b]
Asymp. Sig. (2-tailed)	.001

a. Wilcoxon signed ranks test

b. Based on positive ranks

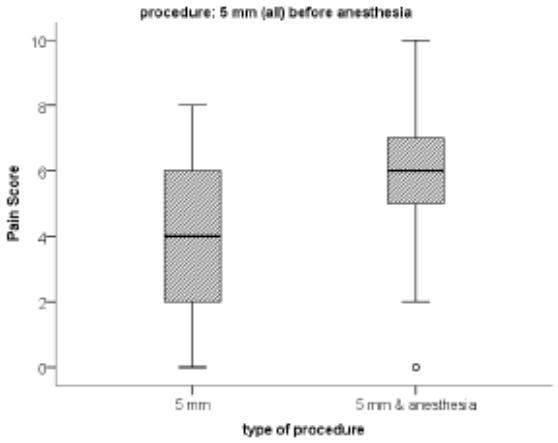

Figure 5. Pain before anesthesia.

This anesthesia technique is inexpensive (1% lidocaine without epinephrine), easy to learn and acts quickly, providing pain relief and comfort to gynecological outpatients. The 35 cm long Cystoscopy Injection Needle is marketed and easily acquirable; pricing in Portugal is around twenty euros per unit.

Main findings

"Hysteroscopic anesthesia" is very effective in lowering pain at hysteroscopy. It is also cheap, simple, very useful for improving tolerance in outpatient hysteroscopy examinations and surgery.

Strengths and limitations

Results showed pain in hysteroscopy can be controlled with this innovative local anesthesia technique. Authors believe that evidence is convincing, accurate, reproducible and can be extrapolated to general population.

Nevertheless authors suggest well-designed randomized controlled

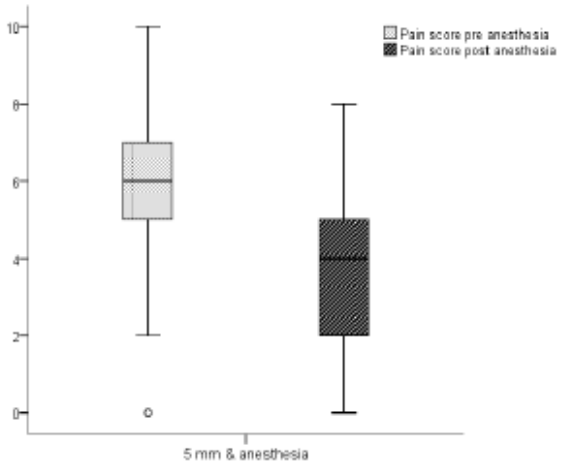

Figure 6. Hysteroscopy (5 mm scope) with and without anesthesia.

trials will most certainly give better evidence of efficacy of this novel technical improvement in hysteroscopy.

Interpretation (findings in light of other evidence)

Pain scores can be reduced by "hysteroscopic anesthesia" and make this procedure tolerable for outpatients.

Conclusions

From evidence gathered we must conclude that "hysteroscopic anesthesia" is very promising both for diagnostic and see and treat approach in outpatients'office hysteroscopy.

It may be especially important in older women who were more likely to complain of discomfort.

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PART III – DISCUSSION AND CONCLUSIONS

1. Discussion

Hysteroscopy as a tool can be used both with a diagnostic and a therapeutic approach. As Mairos et al point out [83], hospitalization exposes patients to adverse event or injury related to medical management and 1 of 10 will suffer damage in contrast to complications of the disease itself [135, 136]. This makes office procedures not only cost effective, but in fact safer for patients and goes in line with WHO Alliance for Patient Safety policy.

Hysteroscopy remains a gold standard technique [137] for diagnostics [137] and surgical treatment of intracavitary lesions [68] [83]. In office setting hysterocopy's main drawback is pain [62, 68, 137] as Favilli et al observe in a comment on our article "Is pain better tolerated with mini-hysteroscopy than with conventional device?" [138]. He does stress out and we concur, that the issue of pain will not be solved exclusively reducing scope size.

Several authors have written on pain reducing techniques [62, 68], with a special focus on using a vaginoscopic "no touch" approach [63, 64, 84, 90, 134, 139, 140] and this points seems settled by Cooper et al in her systematic review as a statistical significance was found between lower pain perception and the vaginoscopic approach [66].

As for analgesia and local anaesthetics, Ahmad's et al Cochrane review of 2010 addresses local anaesthetics (various routes of administration) with conflicting results, NSAID (used in the hypothesis that prostaglandin release may cause pain), buprenorphine, the anti-spasmodic drotaverine hydrochloride combined with mefenamic acid and intravenous sedation in various settings[141]. He concludes there is a statistically significant decrease in pain reporting with local anesthetics, but mean pain reduction is small. Likewise Cooper addresses the issues of topical anaesthetic agents applied locally, or intracervical, paracervical and intrauterine (transcervical local) administration, intramuscular (IM) use of tramadol and use of conscious sedation. Her results show local anesthetic reduce pain experienced during outpatient hysteroscopy when used in paracervical and intracervical injections, but not with transcervical and topical application [72]. She concludes injectable, preferably paracervical, administration of local anesthetic should be used for women undergoing hysteroscopy as outpatients to reduce the amount of pain experienced. Although her conclusions point to usage of these drugs, the strength of her results is small and she does mention the need for large trials to confirm her findings. She also cautions that administration of such drugs may have side effects and results do not include pain relieve in hysteroscopy surgery.

In 2003 De Angelis et al published a paper reporting the use of transcutaneous electrical nerve stimulation (TENS) for pain relieve in hysteroscopy [142]. The rational for this study was that the stimuli would act on large-diameter "A" fibers (according to the "gate control" theory) establishing a blockade or "gating effect" at the dorsal horn of the spinal cord, thus preventing pain from being transmitted to the upper nervous system. They compared seventy one patients in each or the two arms and found a statistical significant difference between groups of users and controls. No other study has confirmed this result in hysteroscopy.

Finally, as to distension media and pain, Pluchino et al [143] and Cicinelli et al [140, 144] found normal saline to be less painful than CO2, but Cooper et al in 2010 published a systematic review where she discussed utility, quality of vision and pain [145]; this study did not support this point of view. It concluded both CO2 and normal saline are adequate for office hysteroscopy and pain did not show statistical difference between either, but as normal saline

allows surgery with bipolar electrodes, it would probably by more convenient if surgery in foreseen.

Lowering pain perception can be done with reduction in the calibre of instruments as several RCT have shown [62, 68, 90, 140, 146, 147], while others [137, 148] could not sanction this effect; there was no systematic review confirming these data. To tackle this question in 2015 we published a paper entitled *"Is pain better tolerated with mini-hysteroscopy than with conventional device? A systematic review and meta-analysis."* Our results showed a statistically significant lowering of pain scores with slenderer scopes (3 to 3.6mm outer sheet diameter) but also suggested there may be a cutoff around 3.5mm below which further reduction in caliber may not result in better tolerance.

Another query which we undertook was to estimate how many women still complained of pain with smaller scopes. We published in 2015 this paper "*What proportion of women refers moderate to severe pain during office hysteroscopy with a mini-hysteroscope? A systematic review and meta-analysis*". To the best of our knowledge this was this first ever study seeking trials or arms within a trial where only the better tolerated "mini-hysteroscope" was used. We reached the conclusion that mini-hysteroscopy remains painful for at least 13 % of women if cut-off for moderate pain is set at VAS ≥ 5 but it reaches over thirty percent if cut-off switches to a more acceptable and consensual value of VAS ≥ 4.

Several clinical and psychological factors have been suggested to influence pain reporting. Menopause is one such factor found associated to higher pain scores [137, 144] while other authors did not find such difference [148]. Previous cesarean section [144] and chronic pelvic pain [144, 149] were found by logistic regression to significantly correlate with higher pain at hysteroscopy, while anxiety showed a mildly significant correlation with pain [144]. But on the other hand Sessa could not find significance in pain in women with history of cesarean section [150]. Operator experience [143, 149] and shorter duration of procure seem to have a protective roll [149]. Body mass index (BMI) may associate with less pain reporting [151]. Vaginal or cervical stenosis can be reason for pain and preclude the completion of hysteroscopy [146, 152]. With our prospective study "Hysteroscopy and pain: what risk factors should we consider in office hysteroscopy? Are there really any?" we tried to answer these questions. We did not find significance in pain reporting through ordered logistic regression with menopause, dysmenorrhea, and history of menorrhagia or parity of women. The only variable we found to have significance was BMI and our conclusion was obesity may have impact on pain, reducing its perception, probably related to higher estrogen levels in overweight women.

Anxiety and its effect on pain at hysteroscopy was studied by Kokanali et al [153] and they found a positive correlation with both STAI-Y1 and STAI-Y2 scores and pain. Additionally they also found significance with in-hospital waiting time for both anxiety and pain scores. One the other hand Carta et al found no significant correlation between anxiety scores and pain reporting [154]; he did find significance, although with a weak correlation, to waiting time greater than sixty minutes and in women who are in menopause. Our results in "*Pain, anxiety and patient satisfaction in office hysteroscopy, is there a link? Are patient satisfaction questionnaires reliable?"* showed no correlation between STAI-Y1 and severity of pain, with a meek influence of STAI-Y2 scores on pain. As to satisfaction questionnaires, they proved to be reliable, with both excellent specificity (72%) and sensitivity (94%). Three answer questionnaires are simple to administer, easy to interpret and may prove be very helpful in

clinical practice (especially in departments where local anaesthesia is administered "if necessary").

Much has been written on local anaesthetics and hysteroscopy, with both systematic reviews from Cooper et al [72] and Ahmad et al [141] finding significance, if small, for pain control in office hysteroscopy and perhaps this is the reason why the Royal College of Obstetricians and Gynaecologists, despite recommending topical, local and transcervical anaesthetics, emphasises that no significant reduction in pain was demonstrated (transcervical application). [155]

In our article *"Office hysteroscopy and pain control, a multicenter comparison by scope size and introducing a novel "hysteroscopic anesthesia" technique"* we emphasize the original mode of administration of the local anaesthetic (which is injected under direct and live view) through the hysteroscope to the exact location where pain is felt during the procedure. This may account for the dramatic change of pain scores before and after injection (via a 35 cm long Cystoscopy Injection Needle).

As to the other conclusions of this trial, we did not find significance between pain felt with mini-hysteroscopy and conventional (5mm) hysteroscopy; however, one should take into account two circumstances: first each Centre only used either 3.5mm or 5mm scopes, and second pain evaluation was done with two different tools (VAS in Viseu and NRS in Lisboa). Finally there is a variation in population: Viseu is mainly a medium sized city with the majority of women being of civilian and rural extraction, while in Lisboa patients are mostly urban, military personnel or their relatives. These biases might influence pain reporting and preclude our expected differences in pain by scope size to show statistical significance.

2. Conclusions:

1) Mini-hysteroscopy is less painful than conventional 5mm hysteroscopy and, in line with RCOG/BSGE recommendations, should be preferred in outpatient diagnostic hysteroscopy [155].

2) Even when mini-hysteroscopy is used, pain may be present in 13% to 30% of women depending on what cutoff we use for mild pain (VAS≥5 or VAS≥4 respectivly).

3) The only predictive factor that showed significance (protecting from pain at hystersocopy) was elevated BMI. Previous cesarean section, menopausal state, history of pelvic pain and dysmenorrhea *do not seem* to influence discomfort. As for cervical surgery and/or stenosis, there were not enough cases represented to support any kind of opinion.

4) Anxiety *may not* be an important factor in pain, even if anxiety trait might have a very slight influence. This could sugest anxious women can benefit from a short-acting anxiolytic such as midazolam.

5) Satisfaction questionnaires seem promissing and reliable for use instead of 10cm VAS or NRS, more complicated to understand by patient. A three question anwer could probably be used in the office and help decide which woman should have local anaesthetic to ease pain.

6) Although further studies are warrented to acertain its utility, *hysteroscopic anaesthesia* seems promising in making the procedure tolerable for most women.

3. Future perspectives:

We recognize changing attitudes is a slow process and physicians always seek hard facts to adjust their protocols. Therefore it is highly desirable that well designed RCT's comparing pain at hysteroscopy with and without *hysteroscopic anaesthesia* be undertaken to evaluate and either attest or refute the benefits of this promising intervention, which we think, may prove very useful.

Assessment of utility of three answer questionnaires and validation of these as a scoring tool in the same RCTs would help corroborate our other findings and bring this simple tool into daily practice.

Finally, risk factors predicting pain at hysteroscopy will probably remain under debate for some time. We do however think, that as soon as a suitable analgesia (or local anaesthesia technique) is in place, the question of risk factors for pain will most likely become obsolete.

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Appendix

Portable CD with work files and authorizations

Applicable legislation and regulations Decree-Law 74/2006 dated March 24, as amended by Decree-Law 107/2008 dated June 25 and Decree-Law 230/2009 dated September 14. Regulation of Studies of the University of Aveiro, regulation 214/2012, DR 2nd series, 109 dated June 5. Regulation of the Doctoral School of the University of Aveiro, order 6403/2011, DR 2 nd series, 74 dated April 14. Regulation for accreditation of training and professional experience at the University of Aveiro, order 7047/2011, DR 2 nd series, 89 dated May 9. Regulation of the Doctoral Programme of Health Sciences and Technologies of the University of Aveiro, order 12177/2010, DR 2 nd series, 145 dated July 28, DGES R/A-Cr 38/2010, accreditation process NCE/09/00462. Regulation of the Health Sciences Department of the University of Aveiro, regulation 641/2010, DR 2 nd series, 145 dated July 28.